Janssen Vaccines & Prevention B.V. *

Clinical Protocol

Protocol Title

A Randomized, Observer-blind, Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Different Dose Levels of Ad26.COV2.S Administered as a One- or Two-dose Regimen in Healthy Adolescents From 12 to 17 Years Inclusive

HORIZON 2

Protocol VAC31518COV3006; Phase 2
AMENDMENT 4

VAC31518 (JNJ-78436735)

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

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

Regulatory Agency Identifier Number(s):

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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 4	This document
Amendment 3	28 February 2022
Amendment 2	26 October 2021
Amendment 1	13 July 2021
Original Protocol	22 January 2021

Amendment 4:

Overall Rationale for the Amendment:

Part 1 of Study VAC31518COV3006 has been ongoing since 29 September 2021. Since the start of enrollment, there has been a slower than desired participant enrollment rate mainly due to the success of the national vaccination programs in the countries where Part 1 is being conducted and a high number of participants being seropositive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at screening/randomization. Thus, the current design of Part 2 in vaccine naïve participants is no longer feasible nor relevant and will, therefore, be removed from this study. However, Part 1 will continue as planned and the results may yield a preferred dose to be used in potential future studies.

A further change introduced in this amendment consists of removal of the booster vaccination (or third active vaccination) for participants initially enrolled to receive 2 active vaccinations in the primary vaccination regimen. This change is performed in order to align participants in all groups to receive 2 active study vaccinations, ie, to have the same vaccination exposure. Also, the follow-up period post last active vaccination was reduced from 12 months to 6 months on the basis of the well-defined vaccine safety profile. Given that approved COVID-19 vaccines exist for the adolescent population in all countries in which VAC31518COV3006 is being conducted, if participants need to receive further boosters, they may be vaccinated outside of the study as a part of their national vaccination campaign after the participants have completed their last study visit.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5, and 6) 3 Objectives and Endpoints 4.1 Overall Design 4.4 End of Study Definition 6.1 Study Vaccine(s) Administered 6.3 Measures to Minimize Bias: Randomization and Blinding 6.8 Study Vaccination Pausing Rules 8.1 Immunogenicity Assessments 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.5 Planned Analyses	Removal of Part 2 of the study throughout the protocol, which included deleting Section 1.3.3 and Section 1.3.4. Subsequent subsections were renumbered accordingly.	See overall rationale for amendment.
Cover page 1.1 Synopsis	Changed to a Phase 2 study	Study is no longer a Phase 2/3 adaptive study

Section Number and Name	Description of Change	Brief Rationale
4.1 Overall Design		as Part 2 has been removed.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2, and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5, and 6) 4.1 Overall Design	Removal of the booster vaccination (or third active vaccination) for participants initially enrolled to receive 2 active vaccinations in the primary vaccination regimen.	To align participants in all groups to receive 2 active study vaccinations.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 1.3.2Part 1: Dose Selection Cohort (Groups 4, 5 and 6) 4.1 Overall Design 4.4 End of Study Definition 10.2 Appendix 2: AESI Clinical Laboratory Tests	The follow-up period post last active vaccination reduced from 12 months to 6 months.	The vaccine has a well-defined safety profile.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2, and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5, and 6) 4.1 Overall Design	Finger-prick test specified to test for SARS-CoV-2 antibodies at screening.	Clarification
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 9.1 Statistical Hypotheses	Vaccine immunogenicity will be compared between study groups in VAC31518COV3006.	Clarification
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization anexplorad Blinding 9.5 Planned Analyses	The primary analysis of safety, reactogenicity and immunogenicity will include data up to 28 days post-dose 2 from which the selected dose level for any future study in adolescents will be determined.	Clarification
1.1 Synopsis 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding	The randomization has been revised to having not more than 70% males or females	To allow more flexibility in recruitment.
1.3.3 Procedures for Participants With (Suspected) COVID-19	Footnote f has been updated in the vaccination schedule table regarding combining visits.	To clarify and limit blood draw volumes if multiple visits overlap in the same windows.
1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5 and 6) 8.2.2 Vital Signs 9.4.2 Primary/Secondary Endpoints	Text has been updated to add preferably supine systolic and diastolic blood pressure in the body and footnote h in the SoA.	Clarification
2 Introduction 2.3.1 Risks Related to Study Participation	Updated reference to the Investigator's Brochure to latest	Update

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 6.1 Study Vaccine(s) Administered 11 References	version (6.0).	
10.2 Appendix 2: AESI Clinical Laboratory Tests	Title changed from Hematology Clinical Laboratory Tests to AESI Clinical Laboratory Tests. Clarification made between local and central laboratory hematology tests. The table for suspected MIS-C AESI assessments merged with the table for suspected TTS AESI assessments.	Clarification
6.3 Measures to Minimize Bias: Randomization and Blinding	Addition of vaccine/dose volume as an example of data that may potentially unblind the vaccine assignment.	Additional example for clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Minor clarifications were also made throughout the protocol.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Observer-blind, Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Different Dose Levels of Ad26.COV2.S Administered as a One- or Two-dose Regimen in Healthy Adolescents From 12 to 17 Years Inclusive

Ad26.COV2.S (also known as Ad26COVS1, VAC31518, JNJ-78436735) is a monovalent vaccine composed of a recombinant, replication-incompetent human Ad26 vector, constructed to encode the SARS-CoV-2 spike (S) protein, stabilized in its prefusion conformation.

The term "adolescents" in this study refers to participants from 12 to 17 years of age inclusive.

OBJECTIVES AND ENDPOINTS

Part 1 Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S administered intramuscularly (IM) as a 1-dose regimen (at 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level) or as a 2-dose (56-day interval) regimen (2.5×10^{10} vp per 0.5 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) in adolescents.	• Solicited local and systemic adverse events (AEs) for 7 days post-dose 1 and 2. • Unsolicited AEs for 28 days post-dose 1 and 2. • Medically-attended adverse events (MAAEs) from the first vaccination until 6 months post-dose 1 or post-dose 2. MAAEs leading to discontinuation will be collected during the entire study. • Serious adverse events (SAEs) from the first vaccination until the end of the study. • Adverse events of special interest (AESIs) from first vaccination until end of the study (incl multisystem inflammatory syndrome in children [MIS-C]).
• To assess the humoral immune response of Ad26.COV2.S administered IM as a 1-dose regimen (at 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level) or as a 2-dose (56-day interval) regimen (2.5×10^{10} vp per 0.5 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) in adolescents.	• Serological response to vaccination as measured by spike-enzyme-linked immunosorbent assay (S-ELISA) (ELISA; Units/mL [EU/mL]) or equivalent assay, or virus neutralization assay (VNA) titers at 28 days post-dose 1 and 14 days post-dose 2.

Part 1 Secondary and Exploratory Objectives and Endpoints

Secondary	
• To assess the humoral immune response to 3 dose levels of Ad26.COV2.S (2.5×10^{10} vp, 1.25×10^{10} vp, or 0.625×10^{10} vp) and regimens in all study groups at all blood collection timepoints.	• Serological response to vaccination measured by binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA (or equivalent assay), and/or • Serological response to vaccination measured by neutralizing antibody titers to SARS-CoV-2 (VNA).
• To assess the safety and reactogenicity of Ad26.COV2.S administered IM as a booster in adolescent participants (Groups 1-3).	• Solicited local and systemic AEs for 7 days post-booster. • Unsolicited AEs for 28 days post-booster. • MAAEs from the booster until 6 months post-vaccination.
• To evaluate the humoral immune response in adolescent participants who receive a booster dose during the study, pre-boost and at selected time points post booster vaccination (Groups 1-3).	• Serological response to vaccination measured by binding (S-ELISA and/or equivalent assay) and/or neutralizing (VNA) antibody titers
Exploratory	
• To examine the immune response in vaccinated adolescents after 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. • SARS-CoV-2-binding antibodies measured by ELISA (or equivalent assay): Analysis of antibodies binding to the SARS-CoV-2 S and/or N protein. • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling in adolescents 12 to 17 years of age.
• To assess the correlation between the binding antibodies (S-ELISA) and neutralizing antibody (VNA) titers to SARS-CoV-2 at selected timepoints.	• Correlation between binding antibodies (S-ELISA; EU/mL, or equivalent assay) and VNA (wtVNA and/or psVNA) titers at selected timepoints.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms in adolescents.	• The number of adolescents with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by the Symptoms of Infection with Coronavirus-19 (SIC).
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• Serologic conversion between baseline (Day 1; pre-vaccination) and selected timepoints post-vaccination using an ELISA and/or

	SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 N protein. • The number of asymptomatic participants with a SARS-CoV-2 positive molecular test. • *For asymptomatic case definition, see Section 10.9.3.*
• To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.	• Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA or equivalent assay.
• To assess the impact of the Ad26.COV2.S vaccine on the incidence of co-infections with SARS-CoV-2 and other respiratory pathogens in adolescents who have received Ad26.COV2.S during the study.	• Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in nasal swab samples from adolescents with a symptomatic infection.
• To assess the presence of SARS-CoV-2 variants during a confirmed COVID-19 episode in adolescents. • To assess SARS-CoV-2 viral load during a confirmed COVID-19 episode in adolescents.	• Identification of SARS-CoV-2 variants by sequencing of nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode. • Analysis of SARS-CoV-2 viral load (via qRT-PCR) in nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode.
• To further explore the humoral immune responses in participants who have received Ad26.COV2.S.	Exploratory analyses may include the following assays: • SARS-CoV-2 neutralization as assessed by VNA. • Adenovirus neutralization as measured by VNA. • Analysis of neutralizing and binding antibodies against emerging SARS-CoV-2 virus lineages. • Functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass and IgG isotype, antibody glycosylation, and assessment of antibody repertoire. • Analysis of antibodies to S, N, and the receptor binding domain (RBD) of the SARS-CoV-2 S protein, and surface proteins of other coronaviruses. • Epitope-specificity characterization of antibodies. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or

	adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. • Seroresponse rates according to different responder definitions.

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 be performed in addition, as outlined in a revised statistical analysis plan (SAP).

Hypotheses

No formal hypothesis testing is planned in Part 1. Descriptive statistics will be used to compare vaccine immunogenicity in adolescents from study VAC31518COV3006 versus vaccine immunogenicity in young adults (18 to 25 years of age) from study VAC31518COV3001 or VAC31518COV3009 and between study groups in VAC31518COV3006.

OVERALL DESIGN

This is a randomized, observer-blind, pivotal Phase 2 study in healthy adolescents from 12 to 17 years of age. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S in a 1- and 2-dose (56-day interval) vaccination regimen will be evaluated. The study will descriptively compare the immune responses measured by S-ELISA (and potentially VNA) in adolescents versus the immune responses measured in young adults from study VAC31518COV3001 (after administration of 1 dose of Ad26.COV2.S) or VAC31518COV3009 (after administration of 2 doses of Ad26.COV2.S) and between study groups in VAC31518COV3006. This study consists of the Dose Selection Cohort, and it is designed with dose and regimen selection performed in 2 Independent Data Monitoring Committee (IDMC) analyses at established timepoints (see Section 10.3.6).

Previously, this study was designed to comprise Part 1 and Part 2, wherein Part 2 included the Extension Cohort of vaccine naïve participants for evaluation of the dose level and dose regimen selected after review of the data in Part 1. Per protocol amendment 4, Part 2 will no longer be conducted.

Participants will receive Ad26.COV2.S as a first dose and Ad26.COV2.S or placebo as a second dose. Ad26.COV2.S will be administered IM at 1 of up to 3 dose levels: 2.5×10^{10} vp, 1.25×10^{10} vp, or 0.625×10^{10} vp. The 2.5×10^{10} vp has been tested before in adolescents, in study VAC31518COV2001. A single dose of Ad26.COV2.S at 2.5×10^{10} vp was administered to a cohort of participants 16 to 17 years of age (33 participants received active vaccine or placebo in a blinded manner, 10:1 ratio). Immunogenicity and safety data in adolescents 16 to 17 years of age and adults from COV2001 were evaluated by an IDMC and the Medicines and Healthcare products Regulatory Agency (MHRA) who allowed a continuation of evaluation in participants of 12 to 15 years of age. This COV3006 study will be evaluating dose levels of 2.5×10^{10} vp and lower in participants from 12 to 17 years of age.

A target of approximately 300 adolescents seronegative for SARS-CoV-2 antibodies at baseline (as assessed by local serology finger-prick testing) will be enrolled in a 2-dose vaccination regimen (56-day interval) with 1 or 2 active vaccinations, with placebo administered as a second dose for those in the 1-dose regimen.

Participants in a Dose Selection Cohort will be randomly assigned in a 1:1:1:1:1:1 ratio to 1 of 6 study arms: (a) to receive one active vaccination of Ad26.COV.2 (either 2.5×10^{10} vp per 0.25 mL dose volume,

1.25×10^{10} vp, or 0.625×10^{10} vp) followed by placebo at Day 56 in a 1-dose regimen (Groups 1, 2, and 3, respectively), or (b) to receive 2 active vaccinations of the same dose level (either 2.5×10^{10} vp per 0.5mL dose volume, 1.25×10^{10} vp or 0.625×10^{10} vp) in a 2-dose (56-day interval) regimen (Groups 4, 5, and 6, respectively). Each group will contain 50 participants, of which approximately 70% need to be 12 to 15 years of age and approximately 30% need to be 16 to 17 years of age. Adolescents will be unblinded to the primary vaccination regimen at 6 months after the first vaccination.

Participants in Groups 1-3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine (Vaccination 1). The booster dose level for all participants in Groups 1-3 will be 2.5×10^{10} vp per 0.5 mL.

Participants in Groups 4-6 will not be administered a booster vaccination, given they will receive 2 active vaccinations in the primary vaccination regimen.

As a part of the COVID-19 program safety oversight, the IDMC will review the data on an ongoing basis, in addition to two study-specific predefined IDMC analyses. A first IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 1. A second IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 2. Selected sponsor members will review group unblinded summaries of those data, as well as any available immunogenicity data up to 28 days post-dose 1 and 14 days post-dose 2.. Based on the review, the sponsor will select the dose level and the regimen for any future pediatric studies (either a 1-dose regimen, a 2-dose regimen, or both regimens). The selection will be based on the safety and reactogenicity data (28 days after each vaccination) and any available immunogenicity data (28 days post-dose 1 for the 1-dose regimen, and 14 days post-dose 2 for the 2-dose regimen). Non-binding guidelines on dose and regimen selection will be described in the SAP. Decision making on the optimal dose and regimen may take into account safety, reactogenicity and immunogenicity data from other Ad26.COV2.S clinical studies (such as that of young adults in study VAC31518COV3001 and study VAC31518COV3009 and adolescents from study VAC31518COV2001).
The randomization will take into account having not more than 70% males or females in each age group, as evenly divided as possible over the different age groups. Stratification is by sex and age group. Screening will ensure participants are seronegative at baseline for SARS-CoV-2 antibodies by utilizing the finger-prick test (by testing blood from a small puncture in the finger).

Table: Part 1 Vaccination Schedules (Dose Selection Cohort)

		Vac 1	Vac 2	Vac 3[d]
Group	**N[a,b,c]**	**Day 1**	**Day 57**	**Day 184**
1	50	2.5×10^{10} vp (0.25 mL)	Placebo	2.5×10^{10} vp (0.5 mL)
2	50	1.25×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
3	50	0.625×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
4	50	2.5×10^{10} vp (0.5 mL)	2.5×10^{10} vp (0.5 mL)	
5	50	1.25×10^{10} vp	1.25×10^{10} vp	
6	50	0.625×10^{10} vp	0.625×10^{10} vp	

N number of participants; Vac vaccination; vp virus particles.
a No more than 70% of males or females should be randomized in each age group.
b All participants must be seronegative for SARS CoV 2 antibodies at baseline.
c Approximately 30% of participants should be between 16 to 17 years age and approximately 70% should be between 12 to 15 years of age.
d Participants in Groups 1 3 will be given a booster vaccination as of 6 months after the last vaccination with the active vaccine (Vaccination 1) and the booster dose level for these participants will be 2.5×10^{10} vp per 0.5 mL.

At the time of study entry, participants or parent(s)/caregiver(s) will need to indicate to the site staff, in case they, or their child, respectively would get infected with SARS-CoV-2, the identity and location of their

routine medical care physician and/or facility where they would obtain emergency care and hospitalization for the participant, if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, participants or parent(s)/caregiver(s) will be recommended to go to the health care professional or hospital that has been identified in advance. For the duration of the study, the participant will be asked through the eCOA, if they have experienced any new symptoms or health concerns that may require seeking emergency care.

All adolescents with COVID-19-like signs or symptoms and adolescents with a positive RT-PCR test from outside the study meeting the prespecified criteria for suspected COVID-19 should undertake the COVID-19 procedures until 14 days after signs or symptom onset/positive RT-PCR test from outside the study (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last, unless it is confirmed that the COVID-19 Day 1 to 3 nasal swab (for those that have it) is negative for SARS-CoV-2. Resolution of the COVID-19 episode is defined as having 1 SARS-CoV-2 negative nasal swab and 2 consecutive days with no COVID-19-related signs or symptoms. The procedures in case of (suspected) COVID-19 are described in the body of the document.

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 shown in the Schedule of Activities for the last participant in the study.

NUMBER OF PARTICIPANTS

A target of approximately 300 adolescents seronegative for SARS-CoV-2 antibodies at baseline (as assessed by local serology finger-prick testing) will be enrolled.

VACCINE GROUPS AND DURATION

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

- Three dose levels of Ad26.COV2.S will be used, 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp. Ad26.COV2.S will be supplied at a concentration of 1×10^{11} vp per mL as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as diluent to prepare the 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level.
- Placebo will be supplied as a 0.9% NaCl solution.

Participants allocated to the 2.5×10^{10} vp dose level in Part 1 will receive 1 of 2 volumes: 0.5 or 0.25 mL. A volume of 0.5 mL will be administered to participants in all other dose groups.

Study duration for participants in Part 1 is approximately 8 months (Groups 4-6) to12 months (Groups 1-3), provided the intervals in the SoA are respected.

IMMUNOGENICITY EVALUATIONS

Blood for evaluation of humoral immune response will be drawn from participants at the timepoints specified in the SoA.

Immunogenicity assessments may include, but are not limited to, the immunogenicity assays (as available and feasible) summarized in the below table.

Table: Summary of Immunogenicity Assays (Part 1)

Assay	Purpose
Supportive of primary endpoints[a]	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to wild-type virus and/or pseudovirion expressing S protein
Supportive of secondary/exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA and/or equivalent assay)	Analysis of antibodies binding to the SARS-CoV-2 S protein, or SARS-CoV-2 variant proteins
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to wild-type virus and/or pseudovirion expressing S protein, or SARS-CoV-2 variants
SARS-CoV-2 binding antibodies (ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to the SARS-CoV-2 N protein
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Binding antibodies to S protein, N protein, RBD of S protein of SARS-CoV-2 and other coronaviruses (MSD, ELISA or equivalent assay)	Analysis of antibodies to S, N, and the RBD of the SARS-CoV-2 S protein or SARS-CoV-2 variants, and coronaviruses other than SARS-CoV-2
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the immune response in serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Gene expression analysis (RNA-seq)	Analysis of gene expression by RNA transcript profiling

ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig = immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; MSD = Meso Scale Diagnostics, LLC; RBD = receptor binding domain; RNA = ribonucleic acid; VNA = virus neutralization assay

a. Either Spike-ELISA or VNA will be used to support the primary endpoint in Part 1.

A rapid SARS-CoV-2 serologic finger-prick test for past infection with SARS-CoV-2 will be performed for all participants at Day 1. Participants who test positive will be informed of the result by the study staff.[a] Participants who test positive will not be included.

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

BIOMARKER EVALUATIONS

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

SAFETY EVALUATIONS

After each vaccination, participants will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) for the presence of any acute reactions and solicited events.

Participants will be asked to note in the reactogenicity diary local 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 reactogenicity 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 reactogenicity diary on a daily basis for 7 days post-vaccination (day of vaccination and the subsequent 7 days), for the following systemic events: fatigue, headache, nausea, and myalgia.

All 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 informed consent/assent form (ICF) is obtained until the end of the study/early withdrawal. Solicited AEs, collected through a reactogenicity diary as part of the eCOA, will be recorded for each vaccination from the time of vaccination until 7 days post-vaccination. Thrombosis with thrombocytopenia syndrome is considered to be an AESI. Suspected AESIs (thrombosis with thrombocytopenia syndrome [TTS] [defined as platelet count below 150,000/µL]) and MIS-C will be reported 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 cases of TTS. All other unsolicited AEs and special reporting situations, whether serious or nonserious, 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) 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. MAAEs are to be reported for all participants from the first vaccination until 6 months after each vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.

STATISTICAL METHODS

Sample Size Determination

The sample size for Part 1 shall enable the selection of the dose and dose schedule for any future pediatric studies.

With a sample size of 50 participants per group, the width of the 90% confidence interval (CI) for the observed proportion of adverse events will vary between 5.8% and 24.8% depending on the observed proportion. Assuming pooling of adverse event data after the first dose of the 1- and 2-dose regimen, the width of this confidence interval will vary between 3% and 17.3% depending on the observed proportion.

Non-binding guidelines on dose and regimen selection will be described in the SAP. Decision making on the optimal regimen will take safety and reactogenicity data, as well as any available immunogenicity data, and data from other Janssen clinical trials of Ad26.COV2.S into account.

A target of approximately 300 adolescents seronegative for SARS-CoV2 antibodies at baseline (as assessed by local serology finger-prick testing) will be enrolled.

Populations for Analysis Set

For purposes of analysis, the following populations are defined:

The Full Analysis Set (FAS) will include all participants with at least one vaccine administration documented.

The Per Protocol Immunogenicity (PPI) 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 samples obtained from participants after SARS-CoV-2 infection (if confirmed by molecular testing or non-S-ELISA [or equivalent assay]) occurring during the study after randomization (if applicable), after other SARS-CoV-2 vaccination outside the study, and samples obtained outside predefined windows will be excluded from the analysis set. Participants who were seronegative by local serology finger-prick test on Day 1 prior to study entry but were determined to be seropositive at baseline by central N- or S- serology testing will also be included in the PPI. More details will be provided in the SAP.

Primary/Secondary Endpoints

Safety

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group and by age group (12 to 15 and 16 to 17 years of age). In addition, for selected tables, tabulations pooled by vaccine dose will also be provided. All safety analyses will be done on the FAS.

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 GMC [ELISA] or GMT [VNA]). 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. More details will be provided in the SAP.

S-ELISA or VNA may be used as endpoint for decision making on dose and regimen selection. Correlation between S-ELISA and VNA and between other relevant humoral immunogenicity readouts will be evaluated.

Planned Analyses

Part 1

A first IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 1.

A second IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 2.

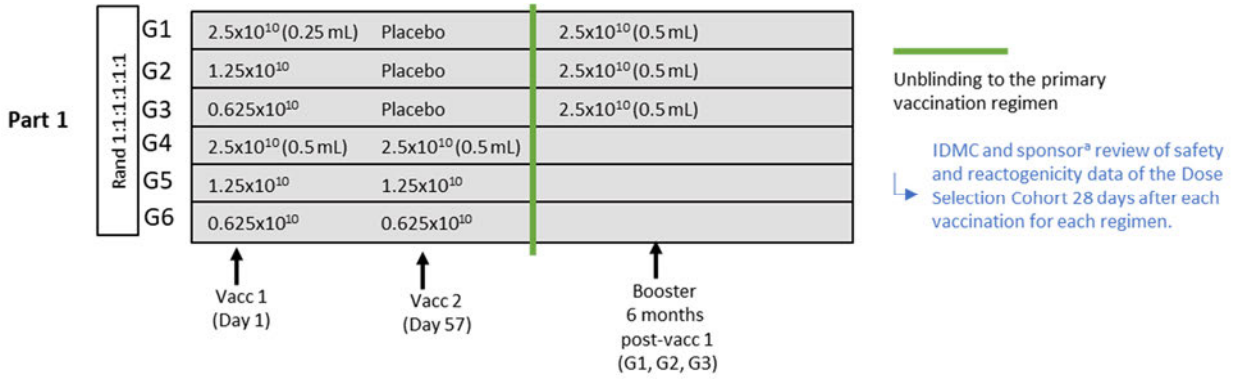
Selected sponsor members will review group unblinded summaries of those data, as well as any available immunogenicity data up to 28 days post-dose 1 and 14 days post-dose 2.

A primary analysis of safety, reactogenicity and immunogenicity data up to 28 days post-dose 2 will be performed and the selected dose level will be determined for any future pediatric studies. The sponsor will be unblinded at the time of the primary analysis, but the blind will be maintained at a participant and study site level up to the unblinding visit. Interim analyses may be performed for safety and/or immunogenicity, to facilitate decision making with regards to planning of future studies or for regulatory submission purposes.

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

1.2. Schema

Figure 1: Schematic Overview of the Study*



G=group; IDMC=Independent Data Monitoring Committee; Rand=randomization; Vacc=vaccination; vp=virus particle

*Note: Study duration for participants in Part 1 is approximately 8 months (Groups 4-6) to12 months (Groups 1-3) provided the intervals in the SoA are respected.

a. Dose Selection Cohort: 50 participants per group will receive 1 or 2 doses of the active vaccine. Participants in Groups 1-3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine (Vaccination 1) and the booster dose level for these participants will be 2.5×10^{10} vp per 0.5 mL. Unblinding to the primary vaccination regimen will take place approximately 6 months after the first vaccination in Part 1.

1.3. Schedule of Activities (SoA)

1.3.1. Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 (SoA visits identical up to Visit 8 for all groups in Part 1)

Phase	Screening	Study Period							At approximately 6 months of study participation						
Visit #	1	2	3	4	5	6	7	8		9	10	11	12	13	Exit[b]
Visit Timing[a]		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d		Vac 1 + 6 m	Vac 3 + 7 d	Vac 3 + 14 d	Vac 3 + 28 d	Vac 3 + 6 m	
Target Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	57-3/+7	64*±2[c]	71*±2	85*±3		Day 184+30 **	Day 191* ±2[c]	Day 198*±3	Day 212*±3	Day 366* ±21	
Visit Type	Screening	Vaccination 1	Safety	Safety (and immuno)	Vaccination 2	Safety	Safety (and Immuno)	Safety		Vaccination 3	Safety	Safety (and Immuno)	Safety	Safety (and Immuno)	Early Exit
Written informed consent/assent[d]	●								Unblinded to primary vaccination regimen[y]						
Inclusion/exclusion criteria	●	●[1]													
Demographics	●														
Medical history/prestudy meds	●														
Physical examination[e]	●														
Pulse oximetry by site staff[f]		●[1]	●	●	●[1]	●	●	●		●[1]	●	●	●	●	
Distribution of pulse oximeter[g]		●													
Vital signs[h] incl. body temperature	●	●[2]	●	●	●[2]	●	●	●		●[2]	●	●	●	●	●[4]
Rapid Serological test for anti SARS CoV 2 antibody (local)[i,j]	●[1]	●[1]													
Nasal swab (centrally)		●								●					
Randomization		●[1]													
Pre vaccination check[k]		●[1]			●[1]					●[1]					
Urine pregnancy test[l]	●	●[1]			●[1]					●[1]					
Blood collection immunogenicity															
Humoral immunity (serum), 10 mL blood draw		●[1]		●	●[1]		●			●[1]		●		●	●[3]

Phase	Screening	Study Period							At approximately 6 months of study participation						
Visit #	1	2	3	4	5	6	7	8		9	10	11	12	13	Exit[b]
Visit Timing[a]		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d		Vac 1 + 6 m	Vac 3 + 7 d	Vac 3 + 14 d	Vac 3 + 28 d	Vac 3 + 6 m	
Target Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	57-3/+7	64*±2[c]	71*±2	85*±3		Day 184+30 **	Day 191* ±2[c]	Day 198*±3	Day 212*±3	Day 366* ±21	
Visit Type	Screening	Vaccination 1	Safety	Safety (and immuno)	Vaccination 2	Safety	Safety (and Immuno)	Safety		Vaccination 3	Safety	Safety (and Immuno)	Safety	Safety (and Immuno)	Early Exit
Blood collection coagulopathy															
Clinical laboratory blood sample, 14 mL (whole blood/ plasma/ serum)[m]		●[1]		●	●[1]		●			●[1]		●			
Vaccination		●			●					●					
Post vaccination observation[n]		●			●					●					
Solicited AE recording		*Continuous*			*Continuous*					*Continuous*					
Unsolicited AE recording[o]		*Continuous (Day 28)*			*Continuous (Day 28)*					*Continuous (Day 28)*					
MAAE recording[p]			*Continuous*												
SAE/AESI recording[q]			*Continuous*												
Concomitant meds[r]			*Continuous*												
Participant reactogenicity diary dispensation and review[s]		●	●			●					●				●[4]
eCOA training and set up[t]		●													
Nasal swab and saliva collection training[u]		●													
Training on AESI symptoms		●													
Distribution of rulers, thermometers, and SIC reference card		●													
SIC, including body temperature of the participant (PROs to be completed by the participant in the eCOA)[v]		●[1]													
(Suspected) COVID 19 surveillance (symptom check)[w]			*Continuous*												

Phase	Screening	Study Period							At approximately 6 months of study participation						
Visit #	1	2	3	4	5	6	7	8		9	10	11	12	13	Exit[b]
Visit Timing[a]		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d		Vac 1 + 6 m	Vac 3 + 7 d	Vac 3 + 14 d	Vac 3 + 28 d	Vac 3 + 6 m	
Target Visit Day ±Window	-28 to 1	1	8±2[c]	29±3	57-3/+7	64*±2[c]	71*±2	85*±3		Day 184+30 **	Day 191* ±2[c]	Day 198*±3	Day 212*±3	Day 366* ±21	
Visit Type	Screening	Vaccination 1	Safety	Safety (and immuno)	Vaccination 2	Safety	Safety (and Immuno)	Safety		Vaccination 3	Safety	Safety (and Immuno)	Safety	Safety (and Immuno)	Early Exit
AESI reminder[x]		*Daily for 30 days after vaccination*			*Daily for 30 days after vaccination*					*Daily for 30 days after vaccination*					

●[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

*The timings of visits after the second and third vaccinations will be determined relative to the actual day of that vaccination, respectively.

** Participants in Groups 1-3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine (Vaccination 1). Participants who have become infected with SARS-CoV-2 during the study after primary vaccination regimen is completed, may receive a booster (3rd) vaccination with the Ad26.COV2.S vaccine, after they have recovered from the acute illness (refer to Section 1.3.3 Procedures for Participants With [Suspected] COVID-19 for definition of recovered) and according to local recommendations on immunization (if available) OR once 1 month has passed since recovery, based on the investigator's judgement.

a. If allowed by local regulations, study visits may take place at the participant's home or other location in the event of ongoing SARS-CoV-2 transmission in the area of the participant. If possible and allowed per local regulation, visits can be performed by a phone call or a telemedicine contact. Except for the screening and vaccination visits, assessments scheduled for the other visits may also be performed by a trained health care professional (HCP), if allowed per local regulations.
b. For those participants who are unable to continue participation in the study up to Visit 13, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who no longer wish to receive study vaccination (see Section 7.1) will be offered all safety and reactogenicity 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 3, or 6 ie, 1 to 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 reactogenicity diary period to review reactogenicity diary information recorded between the actual visit and the end of the reactogenicity diary period.
d. Signing of the ICF/assent should be done before any study-related activity.
e. A full physical examination, including length/height, 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. Pulse oximetry at Day 1 is mandatory, at all other visits only if applicable.
g. Adolescent (12 to 17 years of age) participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.3).

h. Pulse/heart rate, preferably supine systolic and diastolic blood pressure, respiratory rate, and body temperature. Pulse/heart rate measurements should be taken preceded by at least 5 minutes of rest (if feasible) in a quiet setting without distractions (eg, television, cell phones). Vital signs measurements are recommended before blood sampling. Body temperature will be measured preferably orally (routes to be recorded in the eCOA).
i. Rapid serological test for anti-SARS-CoV-2 antibody will collect blood from a small puncture in the finger (finger-prick test at screening).
j. If a rapid serologic test is completed ≤3 days before vaccination, a repeat test is not required on Day 1
k. Investigator must check for clinically significant 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.
l. For participant of childbearing potential only.
m. Whole blood samples will be used for complete blood cell count, including platelet count (hematology, see Section 10.2, Appendix 2), 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 centrally for future testing to evaluate the impact of any potential thromboembolic events. Samples can also be tested (centrally) for anti-PF4 antibodies and platelet activation assay (if HIT/PF4 is positive). Unused samples may be used for immunogenicity testing.
n. After each vaccination, participants will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) for the presence of any acute reactions and solicited events. 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 required minimum post-vaccination observation period is complete.
o. Adverse events 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.
p. MAAEs are to be reported for all participants from the moment of the first vaccination until 6 months after vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study. New onset of chronic diseases will be collected as part of the MAAEs.
q. All SAEs and AESIs 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 and AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure.
r. Concomitant therapies such as, but not limited to, analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from first dose to 28 days post-dose 2 and post-booster (vaccination 3). 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. Concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.4.1 will be collected and recorded in the eCRF from the moment of first vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF from first vaccination through the end of the study.
s. If an event is still ongoing on Day 8 the participant should continue to collect information in the reactogenicity diary until resolution. The reactogenicity diary should be reviewed again at the next visit.
t. Participants will complete the reactogenicity diary using the eCOA on their own eDevice (smartphone or tablet) when feasible. Provisioned devices will be available on a limited basis.
u. Nasal swabs, and saliva (if feasible) during the 7-day cycles may be collected at home by the participant (if sample pick up from the participant's home is feasible).

v. The SIC questionnaire asks the participant if they had any of the prespecified signs or symptoms (see Section 10.7) during the past 24 hours (including highest temperature in the last 24 hours), and (when applicable) to rate the severity. The baseline SIC questionnaire (Visit 2) must be completed the same day as vaccination (ie, to prevent influencing participant responses). If a participant is unable to complete the SIC in the eCOA, a study site staff member can collect information on the participant's behalf as detailed in Section 8.1.2.

w. Participants will be asked, through the eCOA, if they have experienced any new symptoms or health concerns that may require seeking emergency care. Sites should reach out to participants or parent(s)/caregiver(s) if they fail to complete the surveillance question upon any of these reminders. The questionnaire will be accessible on the eCOA platform in between scheduled reminders and participants will be encouraged to answer the surveillance question in the eCOA as soon as possible after the onset of COVID-19-like signs or symptoms. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded. If a participant meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.3, Procedures for Participants With (Suspected) COVID-19.
Enrolled participants and their parent(s)/caregiver(s) will be counselled on SARS-CoV-2 infection prevention each time that they have a contact with site staff, in line with local guidelines.
At the time of study entry, participants or parent(s)/caregiver(s) will need to indicate to the study site, in case they, or their child, respectively would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility where they would obtain emergency care and hospitalization for the participant, if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, participants or parent(s)/caregiver(s) will be recommended to go to the HCP or hospital that has been identified in advance.

x. Participants will be asked daily up to Day 30, through the eCOA, if they experience any new symptoms or health concerns that could be related to TTS or MIS-C (Section 8.3.6).

y. Approximately 6 months after the vaccination 1, participants will be unblinded to the primary vaccination regimen. The IWRS unblinding may occur up to 7 days before the scheduled visit date to allow for appropriate planning and preparations to take place. Participants who do not wish to receive the booster vaccination (vaccination 3) can ask to be withdrawn from the study. An early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent or assent from participation in the study will be offered an optional visit for safety follow-up. This includes the safety assessments of the early exit visit (no blood sampling for immunogenicity [see Section 7.2]). Note that assessments on Visit 9 are to be performed for all participants, irrespective of the outcome of the unblinding.

AE = adverse event; AESI=adverse event of special interest, COVID-19 = coronavirus disease-2019; eCOA = electronic clinical outcome assessment; d = day(s); HCP = health care practitioner; ICF = informed consent form; IWRS = interactive web response system; MAAE = medically-attended adverse event; meds = medication; m = months; MIS-C = multisystem inflammatory syndrome in children; PROs = Patient-reported Outcomes; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19; TTS = thrombosis with thrombocytopenia syndrome; vac = vaccination.

1.3.2. Part 1: Dose Selection Cohort (Groups 4, 5 and 6) (SoA visits identical up to Visit 8 for all groups in Part 1)

Phase	Screening	Study Period							At approximately 6 months of study participation		
Visit #	1	2	3	4	5	6	7	8		9	Exit[b]
Visit Timing[a]		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d		Vac 2 + 6 m	
Target Visit Day ± Window	-28 to 1	1	8±2[c]	29±3	57-3/+7	64*±2[c]	71*±2	85*±3		Day 240±21	
Visit Type	Screening	Vaccination 1	Safety	Safety (and immuno)	Vaccination 2	Safety	Safety (and Immuno)	Safety		Safety (and Immuno)	Early Exit
Written informed consent/assent[d]	●								Unblinded to primary vaccination regimen[y]		
Inclusion/exclusion criteria	●	●[1]									
Demographics	●										
Medical history/prestudy meds	●										
Physical examination[e]	●										
Pulse oximetry by site staff[f]		●[1]	●	●	●[1]	●	●	●		●	
Distribution of pulse oximeter[g]		●									
Vital signs[h] incl. body temperature	●	●[2]	●	●	●[2]	●	●	●		●	●[4]
Rapid Serological test for anti SARS CoV 2 antibody (local)[i]	●[1]	●[1]									
Nasal swab (centrally)		●									
Randomization		●[1]									
Pre vaccination check[k]		●[1]			●[1]						
Urine pregnancy test[l]	●	●[1]			●[1]						
Blood collection immunogenicity											
Humoral immunity (serum), 10 mL blood draw		●[1]		●	●[1]		●			●	●[3]
Blood collection coagulopathy											
Clinical laboratory blood sample, 14 mL (whole blood/ plasma/ serum)[m]		●[1]		●	●[1]		●				
Vaccination		●			●						
Post vaccination observation[n]		●			●						
Solicited AE recording		*Continuous*			*Continuous*						
Unsolicited AE recording[o]		*Continuous (Day 28)*			*Continuous (Day 28)*						
MAAE recording[p]			*Continuous*								
SAE/AESI recording[q]			*Continuous*								
Concomitant meds[r]			*Continuous*								

Phase	Screening	Study Period							At approximately 6 months of study participation		
Visit #	1	2	3	4	5	6	7	8		9	Exit[b]
Visit Timing[a]		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d		Vac 2 + 6 m	
Target Visit Day ± Window	-28 to 1	1	8±2[c]	29±3	57-3/+7	64*±2[c]	71*±2	85*±3		Day 240±21	
Visit Type	Screening	Vaccination 1	Safety	Safety (and immuno)	Vaccination 2	Safety	Safety (and Immuno)	Safety		Safety (and Immuno)	Early Exit
Participant reactogenicity diary dispensation and review[s]		●	●			●					●[4]
eCOA training and set up[t]		●									
Nasal swab and saliva collection training[u]		●									
Training on AESI symptoms		●									
Distribution of rulers, thermometers, and SIC reference card		●									
SIC, including body temperature of the participant (PROs to be completed by the participant in the eCOA)[v]		●[1]									
(Suspected) COVID 19 surveillance (symptom check)[w]					*Continuous*						
AESI reminder[x]		*Daily for 30 days after vaccination*			*Daily for 30 days after vaccination*						

●[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

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

a. If allowed by local regulations, study visits may take place at the participant's home or other location in the event of ongoing SARS-CoV-2 transmission in the area of the participant. If possible and allowed per local regulation, visits can be performed by a phone call or a telemedicine contact. Except for the screening and vaccination visits, assessments scheduled for the other visits may also be performed by a trained health care professional (HCP), if allowed per local regulations.

b. For those participants who are unable to continue participation in the study up to Visit 9, 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 reactogenicity 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 3, or 6 ie, 1 to 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 reactogenicity diary period to review reactogenicity diary information recorded between the actual visit and the end of the reactogenicity diary period.

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

e. A full physical examination, including length/height, 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. Pulse oximetry at Day 1 is mandatory, at all other visits only if applicable.
g. Adolescent (12 to 17 years of age) participants will be provided a pulse oximeter at baseline to measure blood oxygen saturation and pulse rate during a COVID-19 episode (see Section 1.3.3)
h. Pulse/heart rate, preferably supine systolic and diastolic blood pressure, respiratory rate, and body temperature. Pulse/heart rate measurements should be taken preceded by at least 5 minutes of rest (if feasible) in a quiet setting without distractions (eg, television, cell phones). Vital signs measurements are recommended before blood sampling. Body temperature will be measured preferably orally (routes to be recorded in the eCOA).
i. Rapid serological test for anti-SARS-CoV-2 antibody will collect blood from a small puncture in the finger (finger-prick test at screening).
j. If a rapid serologic test is completed ≤3 days before vaccination, a repeat test is not required on Day 1
k. Investigator must check for clinically significant 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.
l. For participant of childbearing potential only.
m. Whole blood samples will be used for complete blood cell count, including platelet count (hematology, see Section 10.2, Appendix 2), 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 centrally for future testing to evaluate the impact of any potential thromboembolic events. Samples can also be tested (centrally) for anti-PF4 antibodies and platelet activation assay (if HIT/PF4 is positive). Unused samples may be used for immunogenicity testing.
n. After each vaccination, participants will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) for the presence of any acute reactions and solicited events. 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 required minimum post-vaccination observation period is complete.
o. Adverse events 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.
p. MAAEs are to be reported for all participants from the moment of the first vaccination until 6 months after vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study. New onset of chronic diseases will be collected as part of the MAAEs.
q. All SAEs and AESIs 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 and AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure.
r. Concomitant therapies such as, but not limited to, analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from first dose to 28 days post-dose 2 and post-booster (vaccination 3). 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. Concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.4.1 will be collected and recorded in the eCRF from the moment of first vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF from first vaccination through the end of the study.

s. If an event is still ongoing on Day 8 the participant should continue to collect information in the reactogenicity diary until resolution. The reactogenicity diary should be reviewed again at the next visit.
t. Participants will complete the reactogenicity diary using the eCOA on their own eDevice (smartphone or tablet) when feasible. Provisioned devices will be available on a limited basis.
u. Nasal swabs, and saliva (if feasible) during the 7-day cycles may be collected at home by the participant (if sample pick up from the participant's home is feasible).
v. The SIC questionnaire asks the participant if they had any of the prespecified signs or symptoms (see Section 10.7) during the past 24 hours (including highest temperature in the last 24 hours), and (when applicable) to rate the severity. The baseline SIC questionnaire (Visit 2) must be completed the same day as vaccination (ie, to prevent influencing participant responses). If a participant is unable to complete the SIC in the eCOA, a study site staff member can collect information on the participant's behalf as detailed in Section 8.1.2.
w. Participants will be asked, through the eCOA, if they have experienced any new symptoms or health concerns that may require seeking emergency care. Sites should reach out to participants or parent(s)/caregiver(s) if they fail to complete the surveillance question upon any of these reminders. The questionnaire will be accessible on the eCOA platform in between scheduled reminders and participants will be encouraged to answer the surveillance question in the eCOA as soon as possible after the onset of COVID-19-like signs or symptoms. Every effort will be made to document the status of all participants that are lost to follow-up due to not completing the eCOA and for whom hospitalization has not been recorded. If a participant meets the prespecified criteria for (suspected) COVID-19 (see Section 8.1.2.1), refer to Section 1.3.3, Procedures for Participants With (Suspected) COVID-19.
Enrolled participants and their parent(s)/caregiver(s) will be counselled on SARS-CoV-2 infection prevention each time that they have a contact with site staff, in line with local guidelines.
At the time of study entry, participants or parent(s)/caregiver(s) will need to indicate to the study site, in case they, or their child, respectively would get infected with SARS-CoV-2, the identity and location of their routine medical care physician and/or facility where they would obtain emergency care and hospitalization for the participant, if necessary. If this information is not available, a plan for where such care could be obtained should be developed. If a participant should have COVID-19 and their symptoms deteriorate, participants or parent(s)/caregiver(s) will be recommended to go to the HCP or hospital that has been identified in advance.
x. Participants will be asked daily up to Day 30, through the eCOA, if they experience any new symptoms or health concerns that could be related to TTS or MIS-C (Section 8.3.6).
y. Approximately 6 months after vaccination 1, participants will be unblinded to the primary vaccination regimen. The IWRS unblinding may occur up to 7 days before the scheduled visit date to allow for appropriate planning and preparations to take place. Participants who do not wish to receive an additional vaccination(s) (Vaccination 2) can ask to be withdrawn from the study. An early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent or assent from participation in the study will be offered an optional visit for safety follow-up. This includes the safety assessments of the early exit visit (no blood sampling for immunogenicity [see Section 7.2]). Note that assessments on Visit 9 are to be performed for all participants, irrespective of the outcome of the unblinding.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; eCOA = electronic clinical outcome assessment; d = day(s); HCP = health care practitioner; ICF = informed consent form; IWRS = interactive web response system; MAAE = medically-attended adverse event; meds = medication; m = months; MIS-C = multisystem inflammatory syndrome in children; PROs = Patient-reported Outcomes; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19; TTS = thrombosis with thrombocytopenia syndrome; vac = vaccination.

1.3.3. Procedures for Participants With (Suspected) COVID-19

Timing relative to onset of signs and symptoms or positive RT-PCR results from outside the study	COVID-19 Day 1 to 3	COVID-19 Day 4 to 7*[a,b,c]	7-Day cycle to be repeated[c,d,e]	COVID-19 Day 29 (±7 d)[c]
Location	Site[g]	Site[g]	Site[g]	Site[g]
Parent(s)/caregiver(s) or participant to contact study site with any health concerns or parent(s)/caregiver(s) or participant notifies the site of becoming aware of a positive RT-PCR test or from a close relative/contact	●			
Site to contact participant if COVID-19 signs or symptoms are recorded in eCOA	●			
Confirmation of suspected COVID-19 using prespecified criteria	●[h]			
Nasal swab and saliva sample[i,j]	●[k,]	●[l]	●[m]	
Humoral immunity (serum), 10 mL blood draw		●[f]		●[f]
RNA-seq (whole blood, PAXgene® tube, 2.5 mL)		●		●
In case of signs and symptoms: SIC, including highest body temperature over the last 24 hours measured by the participants[n] (PROs to be completed by the participant in the eCOA)	*Daily*			●[o]
In case of no signs or symptoms: (Suspected) COVID-19 surveillance (symptom check)	*At least twice a week*			●
Vital signs[p]		●		●
Targeted physical examination		●		●
Pulse oximetry by site staff		●		●
In case of signs and symptoms: pulse oximetry by the participant (PRO to be completed by the participant in the eCOA)[q]	●[k]	*3 times a day*		
Medical history (including recent flu or pneumococcal vaccination) and description of COVID-19 episode (collected by interview with the parent[s]/caregiver[s] or participant)		●		●
Concomitant therapies associated with COVID-19	*Continuous*			
Study-site personnel to contact parent(s)/caregiver(s) or participant	*Weekly or more frequently*			

* Participants with a positive test from outside the study context will immediately proceed with the Day 4 to 7 procedures.

a. The visit at COVID-19 Day 4 to 7 should be scheduled 1 to 6 days after signs or symptom onset and a positive molecular test from COVID-19 Day 1 to 3 or positive RT-PCR test from outside the study.
b. If the nasal swab collected on COVID-19 Day 1 to 3 is negative for SARS-CoV-2, the participant will not undertake any further COVID-19 procedures and will fall back to the default Schedule of Activities in Section 1.3.1, 1.3.2.
c. Only applicable for participants that have a SARS-CoV-2 positive nasal swab from COVID-19 Day 1 to 3 or from outside the study.
d. Participant should be encouraged by the site to have nasal swabs and saliva samples (if feasible) collected from participants (by qualified study site staff/HCP) as indicated in the Schedule of Activities. If the participant is unable or unwilling to have all samples collected as requested, the participant should still complete the other COVID-19 assessments, including the visit at COVID-19 Day 29.

e. Participants should undertake the COVID-19 procedures until 14 days after signs or symptom onset/positive molecular test from outside the study (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last. Resolution of a COVID-19 episode is defined as having 1 SARS-CoV-2 negative nasal swab and 2 consecutive days with no COVID-19-related signs or symptoms. Once past COVID-19 Day 15, collection of nasal swab and saliva samples (if feasible) from participants should be stopped as soon as 1 nasal swab sample is SARS-CoV-2 negative, but (if still symptomatic at that time) the participant should continue completing the PROs (including SIC, body temperature, and pulse oximetry) in the eCOA until 2 consecutive days with no COVID-19-related signs or symptoms.
f. If any of the COVID-19 visits coincide with a scheduled visit in the main SoA, combining the visits is preferred and any blood samples that are listed in both visits should only be collected once. For example: if the COVID-19 visit Day 29 falls within the main SoA Day 29 visit window, visits can be combined and the COVID-19 humoral immunity (serum) sample is not necessary, as a sample will be collected as part of the main SoA Day 29 visit.
g. If a participant has a positive test result for SARS-CoV-2 infection and/or depending on the medical status of the participant, the participant may be requested to not visit the study site (per local or institutional regulations) but to keep the participant at home. If necessary, study-site personnel will visit the participant at home, if allowed by local regulations. Under these circumstances, the participant will be contacted by the site at least once per week to follow-up on the participant's condition and the participant's medical care provider will be notified.
The site staff or HCP visiting the participant at home will use personal protective equipment according to local regulations.
h. In case of COVID-19 like signs or symptoms, based on the information collected through the SIC, the site will reach out to the participant at the latest on COVID-19 Day 2 (the day after the day of signs or symptom onset) to assess whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.2.1). As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19. In case the parent(s)/caregiver(s) or participant would actively reach out to the site already on COVID-19 Day 1, the site should already make a first assessment on COVID-19 Day 1 to check whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Section 8.1.2.1).
i. A nasal swab and saliva sample (if feasible) should be collected from the participant by qualified site staff as soon as the prespecified criteria for suspected COVID-19 are met and, in case of COVID-19 like signs or symptoms, preferably on the day of sign/symptom onset or in the 2 days thereafter (COVID-19 Day 1 to 3). In case of a positive molecular test, a saliva sample (if feasible) should be collected on COVID-19 Day 4 to 7 and nasal swabs and saliva samples (if feasible) should also be collected once every 7 days thereafter until 14 days after signs or symptoms onset/positive RT-PCR test from outside the study (COVID-19 Day 15, if applicable) or until resolution of the COVID-19 episode, whichever comes last. If the nasal swab and saliva sample (Day 1 to 3, 7-day cycle) is collected at the participant's home, site staff should arrange transfer of the sample(s) to the study site as soon as possible after collection. Details are provided in the laboratory manual.
j. All nasal swabs will be tested by a local laboratory for case management. For participants with suspected COVID-19 after a positive local test, confirmation of SARS-CoV-2 infection by a central laboratory will be used for the analysis of the case definition. Nasal swabs will also be used to determine SARS-CoV-2 variants and the viral load. Nasal swabs may also be tested for the presence of other respiratory pathogens using a broad respiratory pathogens panel.
k. The nasal swab and saliva sample (if feasible) should be collected and pulse oximetry 3 times a day should be started (if not started already) as soon as possible after it has been confirmed that the prespecified criteria for suspected COVID-19 (Section 8.1.2.1) are met.
l. Saliva sample for all participants (if feasible), nasal swab only for participants who had a positive RT-PCR test from outside the study.
m. Nasal swabs and saliva (if feasible) during the 7-day cycles may be collected at home by the participant (if sample pick up from the participant's home is feasible). It should be ensured that the participant has sufficient supplies.
n. Participants should complete the (suspected) COVID-19 surveillance (symptom check). In case of COVID-19 like signs and symptoms, participants should be encouraged by the site to complete the SIC daily, preferably in the evening around the same time each day, starting on the first day the participant experiences signs or symptoms. Sites should remind the participant to complete the SIC, unless special circumstances occur such as hospitalization or ventilation, in which case the reason for not completing the SIC should be recorded by site staff in the clinical database.
If a participant is unable to complete the eCOA, a site staff member can collect information on the participant's behalf as detailed in Section 8.1.2.
Participants should measure body temperature daily (in accordance with the local standard of care).

o. If the participant does not have signs or symptoms at that time, the participant will only need to complete the (suspected) COVID-19 surveillance (symptom check).
p. Includes measurement of heart rate, respiratory rate [after at least 5 minutes rest, if feasible], and body temperature. It is recommended that vital signs are measured before collection of nasal swabs or saliva samples and blood draws.
q. In case of COVID-19 like signs or symptoms, the participant will be asked to measure blood oxygen saturation and pulse rate at home 3 times a day (preferably in the morning, at lunch time, and in the evening). The results will be recorded by the participant in the eCOA. On the first day the participant experiences signs/symptoms, the participant should record at least 1 of the 3 pulse oximetry readings in the last 24 hours in the eCOA.

Upon closure of the COVID-19 episode and procedures, all participants will fall back to the default Schedule of Activities (Section 1.3.1, 1.3.2). If the participant experiences new signs or symptoms suggesting possible COVID-19 at a later point in time, the participant would restart the COVID-19 procedures from COVID-19 Day 1 onwards.

COVID-19 = coronavirus disease-2019; d = day(s); eCOA = electronic clinical outcome assessment; PROs = Patient-reported Outcomes; RNA = ribonucleic acid; RT-PCR = real time reverse-transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SIC = Symptoms of Infection with Coronavirus-19

1.3.4. Participants With an AESI

1.3.4.1. Thrombosis With Thrombocytopenia Syndrome

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, ASH 2021, BSH 2021, CDC 2021a). 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, thrombocytopenia, or TTS, local laboratory assessments might be needed 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 laboratory blood sample (whole blood/plasma/serum), 15 mL[d]	●	●
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). Refer to the laboratory manual for further details. For the follow-up visit, the volume of blood to be collected may vary depending on the clinical evaluation of the case. If any of the AESI visits coincide with a scheduled visit in the main SoA or COVID-19 SoA, combining the visits is preferred, when feasible, and any blood samples that are listed in both visits should only be collected once. For example: if the AESI visit Day 29 falls within the main SoA Day 29 visit window, visits can be combined and the Clinical laboratory blood sample (15 mL, whole blood/serum/plasma) is not necessary, as a sample will be collected as part of the main SoA Day 29 visit.
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 10.12 for further details.
f. Refer to Section 6.7 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

1.3.4.2. Multisystem Inflammatory Syndrome in Children (MIS-C)

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 laboratory blood sample (whole blood/plasma/serum), 15 mL[d]	●	●
MIS-C 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). Refer to the laboratory manual for further details. For the follow-up visit, the volume of blood to be collected may vary depending on the clinical evaluation of the case. If any of the AESI visits coincide with a scheduled visit on the main SoA or COVID-19 SoA, combining the visits is preferred, when feasible, and any blood samples that are listed in both visits should only be collected once. For example: if the AESI visit Day 29 falls within the main SoA Day 29 visit window, visits can be combined and the Clinical laboratory blood sample (15 mL, whole blood/serum/plasma) is not necessary, as a sample will be collected as part of the main SoA Day 29 visit.
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 for further details.
f. Refer to Section 6.7 for collection and recording of concomitant therapies associated with a suspected AESI.

AE = adverse event; AESI = adverse event of special interest; MIS-C = multisystem inflammatory syndrome in children.

2. INTRODUCTION

Ad26.COV2.S (also known as Ad26COVS1, VAC31518, JNJ-78436735) is a monovalent vaccine composed of a recombinant, replication-incompetent human Ad26 vector, constructed to encode the SARS-CoV-2 spike (S) protein, stabilized in its prefusion conformation.

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

For the most comprehensive nonclinical and clinical information regarding Ad26.COV2.S, refer to the latest version of the Investigator's Brochure (IB) for Ad26.COV2.S (IB Ad26.COV2.S 2022). As the IB might be further updated after protocol finalization, refer to the latest version of the IB (and addenda, if applicable) for the most recent information.

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

The term "legal guardian" used throughout the document refers to the parent(s) (preferably both if available or 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. For the purposes of this study, all references to participants refer to the participants (adolescents) 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.

The term "caregiver" refers to the delegated primary caregiver(s) who will be responsible for ensuring the study activities are conducted per protocol, eg, accompany the participant to the study site on each assessment day according to the Schedule of Activities (SoA); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; help the study-site personnel ensure follow-up. This person may be the legal guardian, or another appropriate person delegated by the legal guardian.

The term "adolescents" when referring to the participants in this study are 12 to 17 years of age inclusive.

COVID-19 Vaccine and Considerations

Currently, there is only limited availability of authorized vaccines for the prevention of COVID-19 in the pediatric population. The continued development of safe and effective COVID-19 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 SARS-CoV and MERS-CoV S protein have been associated with protection against experimental SARS-CoV and MERS-CoV infection in

nonclinical models (Chen 2005; Zhao 2017). 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 (Letko 2020; Lu 2020; Zhou 2020). Therefore, a neutralizing antibody response against the SARS-CoV-2 S protein may also have a protective effect.

Adenoviral-vectored Vaccines

Recombinant, replication-incompetent adenoviral vectors are attractive candidates for expression of foreign genes for a number of reasons. The adenoviral genome is well characterized and comparatively easy to manipulate. Adenoviruses exhibit broad tropism, infecting a variety of dividing and non-dividing cells. The AdVac® vector platform, developed by Crucell Holland B.V. (now Janssen Vaccines & Prevention B.V.) allows for high-yield production of replication-incompetent adenovirus vectors, eg, Ad26, with desired inserts. The adenovirus E1 region is deleted to render the vector replication-incompetent and create space for transgenes, with viral replication taking place in cells that complement for the E1 deletion in the virus genome. Ad26 has been selected as a potential vaccine vector because there is substantial nonclinical and clinical experience with Ad26-based vaccines that demonstrate their capacity to elicit strong humoral and cellular immune responses and their acceptable safety profile, irrespective of the antigen transgene (see also Section 2.3.1).

The immunogenicity profile of other Ad26-based vectors is illustrated by data obtained following the immunization of adults with HIV vaccines (Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV), an Ebola vaccine (Ad26.ZEBOV), respiratory syncytial virus (RSV) vaccines (Ad26.RSV.FA2 and Ad26.RSV.preF), a Zika virus vaccine (Ad26.ZIKV.001), and a malaria vaccine (Ad26.CS.01). Antigen-specific antibody responses are observed in almost all participants after one dose, in both naïve and pre-immune individuals (RSV). These antibodies may persist for a year or more (RSV) after a single dose in pre-immune participants. They have functional properties of neutralization (RSV, Zika), Fc-mediated antibody-dependent cell-mediated cytotoxicity and antibody-dependent cell-mediated phagocytosis (HIV, malaria). Furthermore, these data support an immunogenicity profile with emphasis on T helper (Th)1 responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha production in CD4+ and CD8+ T cells (Barouch 2013; Milligan 2016; Mutua 2019; Janssen Vaccines & Prevention B.V. Data on file).

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 (Chen 2005; Faber 2005; Modjarrad 2019). 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 (Zumla 2016).

In this study, a 1-dose vaccination regimen at the 2.5×10^{10} virus particles (vp), 1.25×10^{10} vp, and 0.625×10^{10} vp dose level and a 2-dose (56-day interval) vaccination regimen at the 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level will be evaluated in adolescents 12 to 17 years of age.

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

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA Betacoronavirus (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020; Wu 2020). It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019 (Chen 2020; Li 2020). 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 (Lu 2020; WHO 2020c). 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 (Lu 2020; Zhou 2020).

SARS-CoV-2 has spread rapidly and globally since its emergence. The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on 30 January 2020 and declared the outbreak to be a pandemic on 11 March 2020 (WHO 2020a; WHO 2020c). As of 21 January 2021, approximately 96,984,258 cases and 2,077,803 deaths from COVID-19 have been reported worldwide (Johns Hopkins CSSE 2021).

Respiratory symptoms of COVID-19 typically appear 5 to 6 days following exposure to the virus, but may appear from 2 to 14 days following exposure, with the clinical manifestations ranging from mild symptoms to severe illness or death (CDC 2020b; Guan 2020; Linton 2020; UC San Diego Health 2020; WHO 2020b). Severe or critical illness has been reported in 4% of pediatric cases based on a systematic review (Meena 2020) and meta-analysis (Mantovani 2020) of 4,857 and 2,855 children, respectively (ECDC 2020b). Descriptions of COVID-19 clinical case definitions compiled by the US Centers for Disease Control and Prevention (CDC) and Janssen-sponsored interviews with COVID-19-experienced clinicians include the following: 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. Other less common gastrointestinal symptoms have been reported by CDC (nausea, vomiting, diarrhea) (CDC 2020j).

At present, it appears that individuals aged 65 years or older, especially those with comorbidities, such as cardiovascular disease, diabetes, hypertension and underlying pulmonary disease, are subject to the highest incidence of morbidity and mortality (CDC 2020h; Garg 2020; Verity 2020).

Clinical manifestations of disease are less severe in children than adults, with the majority of cases reported as being asymptomatic, mild or moderate (CDC 2020e, Deming 2006, Dong 2020). A study of 149,082 COVID-19 cases reported in the US found that only 1.7% of these cases occurred in persons aged <18 years, with relatively few pediatric COVID-19 cases hospitalized, indicating that COVID-19 might have a mild course among younger patients. Analysis of the COVID-NET found that, one third of children hospitalized with COVID-19 were admitted to the intensive care unit (ICU), while estimates of ICU admission of children hospitalized with seasonal influenza virus infection ranged from 16% to 25%. The case-fatality rate remains low though, even among children hospitalized with more severe COVID-19 associated complications (Kim 2020; Collins 2019). Recent reports have also described several cases of MIS in children with Kawasaki disease-like features (ie, fever, laboratory markers of inflammation, severe illness requiring hospitalization, multisystem organ involvement). As of May 2020, approximately 230 suspected cases of MIS associated with SARS-CoV-2 infection have been reported in EU/EEA countries and the UK, including 2 fatalities (1 in the UK and 1 in France) (ECDC 2020c). As of 08 January 2021, 1,659 confirmed pediatric cases of MIS have been reported to the CDC in the US and 26 deaths, with the majority (~85%) of these cases occurred in children >1 year to 14 years, with an average age of 8 years. Almost all (1,638/1,659 cases) children with MIS had tested positive for current or recent SARS-CoV-2 infection, while the remaining 1% had been in contact with a COVID-19 case. Most children developed MIS 2 to 4 weeks after infection with SARS-CoV-2. It is currently unknown if MIS is specific to children or if it may also occur in adults as it has been reported up to an age of 20 years old (CDC 2020g; CDC 2020d; Verdoni, 2020).

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 (Anderson 2020). In addition, evidence points to Hispanic and Black children likely being at increased risk for severity of COVID-19 infection (Feldstein 2020; Goyal 2020; Kim 2020).

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 one of the most important tools to help control this highly contagious respiratory virus.

2.1. Study Rationale

Detailed information about the rationale for the selected doses can be found in Section 4.2.

Although children appear to be at lower risk of developing severe COVID-19 and death is rare (Dong 2020), children can develop serious complications such as MIS (CDC 2020g; ECDC 2020c; Verdoni, 2020). Children with underlying conditions and those with immune deficiency or who are immunocompromised are at higher risk for severe disease (CDC 2020c). Also, recent studies suggest that children are likely to be important vectors of community spread, including

SARS-CoV-2 transmission from young children in childcare settings and have higher levels of viral load than adults (Heald-Sargent 2020; Yonker 2020; Lopez 2020). The availability of a COVID-19 vaccine for the pediatric population is therefore warranted.

The sponsor is developing a COVID-19 vaccine based on a human replication-incompetent Ad26 vector encoding the SARS-CoV-2 S protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate coronavirus vaccines against SARS-CoV (2003 outbreak), and the common conclusion that has emerged from the evaluation of several different vaccines is that the viral S protein is the only significant target for neutralizing antibodies (Buchholz 2004; Sui 2005; Zhang 2004; Zhou 2004) and the only viral protein that can elicit protective immunity in animal models (Berry 2004; Bisht 2004; Bukreyev 2004; Subbarao 2004; Yang 2004). Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen.

Available platform data, as well as initial immunogenicity and safety data from the first-in-human study VAC31518COV1001 (COV1001) and the Phase 2a study VAC31518COV2001 have demonstrated Ad26.COV2.S at the 5×10^{10} vp and 1×10^{11} vp dose level induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile (Sadoff 2021a), support initiating evaluation of Ad26.COV2.S in the pediatric population, with the dose level 2.5×10^{10} vp (see Section 2.2 and Section 2.3.1). The most extensive safety information of the single-dose regimen of Ad26.COV2.S at 5×10^{10} vp is available from ≥43,000 participants, 18 years of age and above, including adults 60 years of age and above, enrolled in the ongoing pivotal Phase 3 study COV3001. A 2-dose vaccine regimen of Ad26.COV2.S at 5×10^{10} vp is currently under evaluation in the ongoing Phase 3 study COV3009. Supportive safety information (AEs, clinical laboratory abnormalities, vital signs and physical examination findings) is available from the interim analysis of the Phase 1 and 2 studies COV1001, COV1002, and COV2001. In COV2001, Ad26.COV2.S is being evaluated at a range of doses and intervals (1.25×10^{10} vp, 2.5×10^{10} vp, 5×10^{10} vp, and 1×10^{11} vp) in adolescents 12 to 17 years of age, adults 18 to 55 years of age and 65 years of age and above. Ad26.COV2.S has an acceptable safety and reactogenicity profile when administered as a single-dose or as a 2-dose regimen in adults 18 years of age and above, including adults 60 years of age and above. Immunogenicity and safety data in adolescents 16 to 17 years of age and adults from COV2001 were evaluated by an Independent Data Monitoring Committee (IDMC) and the Medicines and Healthcare products Regulatory Agency (MHRA) who allowed a continuation of evaluation in participants of 12 to 15 years of age. While the IDMC endorsed further enrollment of adolescents that would receive Ad26.COV2.S at a 5×10^{10} vp dose level, Janssen (the Sponsor) has decided not to evaluate the 5×10^{10} vp dose in the pediatric population based on the immunogenicity data from the 2.5×10^{10} vp dose in Study VAC31518COV2001 and has decided to redesign the pediatric studies. Therefore, this study protocol has been modified, also taking health authority feedback on the original VAC31518COV3006 study protocol into account. This study will focus on adolescent participants 12 to 17 years of age, and no further enrollment of this age group will take place in VAC31518COV2001. The 33 adolescent participants already enrolled in Study VAC31518COV2001 will continue to be followed for safety and immunogenicity.

Ad26.COV2.S will be evaluated in the pediatric population through a dose-confirmation approach. In the present study (COV3006), the safety and immunogenicity of Ad26.COV2.S will be assessed at a 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level in a 1- and 2-dose (56-day interval) regimen in adolescents from 12 to 17 years of age. Furthermore, it will be determined if the 2.5×10^{10} vp per 0.25 mL dose volume has an acceptable safety profile and similar immunogenicity compared with a 2.5×10^{10} vp per 0.5 mL dose volume. This comparison will generate safety, reactogenicity, and immunogenicity data at a lower injection volume of the currently approved and available Ad26.COV2.S vaccine.

Enrollment of the age groups will start simultaneously (16 to 17 years of age and 12 to 15 years of age). Within each age group, enrollment for all dose levels will start simultaneously for both the 1- and 2-dose regimens. Note that if it is deemed more appropriate to continue with a lower dose level than either 2.5×10^{10} vp or a 1.25×10^{10} vp dose level, then the use of these doses may be removed in a future protocol amendment.

2.2. Background

Nonclinical Pharmacology

Nonclinical pharmacology of Ad26.COV2.S was evaluated in murine, rabbit, Syrian hamster, and nonhuman primate (NHP) animal models for immunogenicity, including assessment of immunological parameters relevant to the theoretical risk of vaccine associated enhanced respiratory disease (VAERD). In addition, vaccine efficacy of Ad26.COV2.S including lung histopathology assessment was evaluated in Syrian hamsters and NHPs. Details are provided in the IB (IB Ad26.COV2.S 2022).

Nonclinical Safety

Biodistribution

To assess distribution, persistence, and clearance of the Ad26 viral vector platform, 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 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. A biodistribution study specifically with Ad26.COV2.S has not been performed.

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). A combined GLP repeated dose toxicity and local tolerance study with Ad26.COV2.S is currently ongoing in New Zealand White rabbits.

Reproductive and Developmental Toxicology

A GLP compliant combined embryo-fetal and pre- and postnatal development study is currently ongoing with Ad26.COV2.S in female NZW rabbits. A draft report of this study is expected in December 2020, while the final report is expected to be issued in January 2021. In this study, female NZW rabbits are injected IM with a control solution (0.9% sodium chloride) or 1×10^{11} vp (2 times the human dose) Ad26.COV2.S on Day 1 (ie, 7 days prior to mating), Gestation Day (GD) 6 and GD 20. The study includes 2 subgroups: 1 group consisting of animals that are necropsied on GD 29 and have a uterine and fetal examination (external, visceral, and skeletal exams), and 1 group consisting of animals that are allowed to give birth and in which the survival and development of the kits is evaluated through Lactation Day 28. An immunogenicity assessment of maternal and fetal/kit serum will be performed to confirm maternal transfer of antibodies.

A further GLP compliant combined embryo-fetal and pre- and postnatal development study has been conducted in female NZW rabbits using an Ad26-based Ebola vaccine, ie, Ad26.ZEBOV (Ad26 vector encoding the glycoprotein of Zaïre ebolavirus Mayinga variant) in a 2-dose regimen with MVA-BN-Filo (Study TOX11212). This study is considered to provide supportive reproduction and development toxicity data for Ad26.COV2.S, as Ad26.ZEBOV is produced from the same Ad26 vector backbone as Ad26.COV2.S.

In study TOX11212, the first vaccination with either Ad26.ZEBOV (1×10^{11} vp) or MVA-BN-Filo (3.61×10^{8} Inf U) was administered 8 days prior to mating female rabbits with untreated male rabbits. This was followed by a second vaccination with either vaccine component 6 days after mating (ie, on GD 6) to maximize exposure of the developing embryo or fetus to the vaccine-induced (maternal) immune response. The study also included a study group that received Ad26.ZEBOV in a homologous regimen, ie, these rabbits received 2 doses of Ad26.ZEBOV. Half the females (Study Phase 1) were necropsied on GD 29 and a uterine and fetal (external, visceral, and skeletal) examination was conducted. The remaining females (Study Phase 2) were allowed to give birth and raise their offspring until weaning; the survival and development of the pups were evaluated through Lactation Day 28.

No adverse effect of Ad26.ZEBOV or MVA-BN-Filo was seen on reproductive performance, fertility, litter data (corpora lutea count, number of implantation sites, viable fetuses, litter size, pre- and post-implantation loss, and number of resorptions), parturition, or macroscopic

evaluations in parental females. Similarly, no adverse effect of vaccination was seen on fetal body weights, external, visceral, and skeletal evaluations or first filial generation pup evaluations from Lactation Day 0 to 28 (sex ratios, survival, body weights, clinical findings, developmental evaluations, and macroscopic evaluations). The vaccine regimens elicited detectable maternal antibody titers that were transferred to the fetuses.

In conclusion, the Ad26.ZEBOV (tested alone or in a regimen with MVA-BN-Filo) did not induce maternal or developmental toxicity in rabbits following maternal exposure during the premating and gestation period.

Clinical Studies

At the time of protocol writing, Phase 1/2a (COV1001, COV1002) and Phase 2a (COV2001) clinical studies to assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S, as well as Phase 3 (COV3001, COV3009) clinical studies to assess the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed moderate to severe/critical COVID-19 in adults are ongoing and data from interim analyses from these studies are available. These data demonstrate that a single-dose of Ad26.COV2.S at 5×10^{10} vp and 1×10^{11} vp induces an immune response that meets prespecified minimum criteria and has an acceptable safety profile (Sadoff 2021a). Data from study COV1001 supports the evaluation of Ad26.COV2.S vaccine in younger age groups. In COV2001, single dose of Ad26.COV2.S at 2.5×10^{10} vp was administered to a limited number of participants 12 to 17 years of age (33 participants received active vaccine or placebo in a blinded manner, 10:1 ratio) (see Section 2.1).

Refer to the latest IB for a high-level description of all ongoing studies with Ad26.COV2.S.

Clinical Safety Experience With Ad26-based Vaccines

Safety of other Ad26-vectored vaccines has been evaluated in adults in other studies by the sponsor. Replication-incompetent Ad26 is being used as a vector in the development of vaccines against diseases such as malaria, RSV, HIV, Zika virus, and filovirus, and has been used in the now licensed Ebola virus vaccine (Zabdeno/Ad26.ZEBOV).

As of 21 December 2020, Ad26-based vaccines developed by the sponsor have been administered to approximately 193,000 participants. The majority of these participants (more than 153,000) are enrolled in an ongoing Ebola vaccine study in the Democratic Republic of the Congo and an ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign) and approximately 35,000 participants are enrolled in other ongoing studies.

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. The studies used the following Ad26-based vaccines: Ad26.ZEBOV (Ebola program; 10 studies), Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV program; 8 studies), Ad26.CS.01 (malaria program; 1 study), Ad26.RSV.FA2 and Ad26.RSV.preF (RSV program; 6 studies), and Ad26.Filo (filovirus program; 1 study) (AdVac Safety Database V5.0 2020). In these 26 studies, 4,224 adult

participants were vaccinated with an Ad26-based vaccine and 938 adult participants received placebo. A total of 6,004 Ad26-based vaccine doses were administered to adults. Most adult participants (3,557 out of 4,224; 84.2%) received Ad26-based vaccine at a dose level of 5×10^{10} vp, while 284 adult participants (6.7%) received Ad26-based vaccine at the 1×10^{11} vp dose level (ie, the highest dose level tested).

As of 21 December 2020, more than 188,000 participants were enrolled in ongoing studies and the ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign). However, their safety data were not included in the AdVac® safety database report V5.0 either because the studies were still blinded, the studies were unblinded but their analysis took place after the AdVac® safety database report cut-off date, or the study data were not integrated in the Ad26 based vaccine database used for the report.

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

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 (Chin 1969; Fulginiti 1969; Kapikian 1969; Kim 1969). 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 Th2-skewed type T-cell response (Moghaddam 2006).

VAERD has also been described for SARS-CoV and MERS-CoV in some animal models, in which candidate vaccines induced a Th2-biased immune response (Agrawal 2016; Bolles 2011; Deming 2006; Honda-okubo 2015; Houser 2017, Smatti 2018), but proof of human SARS-CoV or MERS-CoV VAERD does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. For SARS and MERS, the mechanism of ERD 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, ERD 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-skewed immune response, also induction of a high proportion of neutralizing antibodies compared with virus binding antibodies is desirable to prevent predisposition to ERD as observed for RSV vaccines.

While VAERD was observed in nonclinical studies with experimental SARS and MERS vaccines, it is not a given that the same risk applies to COVID-19 vaccines. To the sponsor's knowledge, antibody-related COVID-19 disease enhancement has not been observed in nonclinical models

yet. Antibodies against the receptor binding domain of SARS-CoV-2 were shown not to enhance in vitro infectivity. Repeated SARS-CoV-2 challenge of NHP or NHP studies with Th2-biasing COVID-19 vaccines that would be expected to predispose to enhanced disease did not show any signs of enhanced disease. In addition, disease enhancement was not observed in NHP immunized with ChAdOx1 encoding SARS-CoV-2 S protein prior to challenge with SARS-CoV-2 (IB Ad26.COV2.S 2022). The Ad26 vector was chosen due to its ability to induce humoral and strong cellular responses with a Th1 immune phenotype (Anywaine 2019; Barouch 2018; Colby 2020; Milligan 2016; Salisch 2019; Stephenson 2020; van der Fits 2020; Widjojoatmodjo 2015; Zahn 2012). 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 IFN-γ and TNF-α production in $CD4^+$ and $CD8^+$ T cells (Anywaine 2019; Barouch 2013; Barouch 2018). In Study COV1001, initial data showed that Ad26.COV2.S induced cellular immune responses as assessed by intracellular cytokine staining and ELISpot. Robust CD4+ T and CD8+ T-cell responses were seen following a single vaccination with Ad26.COV2.S at the 5×10^{10} vp and 1×10^{11} vp dose levels. Following vaccination, CD4+ T cells had a Th1-skewed phenotype and no, or very limited, Th2 responses were observed. The Th1/Th2 ratio was above 1 (median of 7.60 for 5×10^{10} vp and 10.24 for 1×10^{11} vp Ad26.COV2.S) in all participants with a positive CD4+ T-cell response (Sadoff 2021a).

Ad26-based Vaccines in the Pediatric Population

Ad26.RSV.preF in Toddlers:

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 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 dosing.

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 (5×10^{10} vp) vaccine as Dose 1 of the heterologous Ebola vaccine regimen, which also includes MVA-BN-Filo (1×10^{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, SAEs considered related to study vaccine, or AEs leading to discontinuation were reported in children or adolescents.

In the mass vaccination campaign in Rwanda (UMURINZI), 9 SUSARs of febrile seizures have been reported in toddlers within 5.5 to 8.5 hours after vaccination with Ad26.ZEBOV (reporting rate of 3.98 per 10,000 persons).

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 (IB Ad26.COV.2.S 2022).

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

At the time of initial protocol writing, the post-Dose 1 safety and reactogenicity profiles of Ad26.COV2.S (5×10^{10} and 1×10^{11} vp) were considered acceptable, as demonstrated in the interim analyses of blinded safety data from approximately 800 participants (18 to 55 years of age [Cohort 1a (377 participants)] and Cohort 1b (25 participants)] and ≥65 years of age [Cohort 3 (403 participants)]) in the first-in-human study VAC31518COV1001 (Sadoff 2021a). Local solicited adverse events (injection site) were observed in 58.9%, 52.0% and 36.0% of participants in Cohort 1a, 1b and Cohort 3, respectively. Solicited systemic adverse events were reported in 63.7%, 72.0% and 44.9% of participants in Cohorts 1a, 1b, and Cohort 3, respectively. Fevers

(pyrexia, defined as oral body temperature ≥38.0°C/100.4°F) occurred in 19.1% (5.6% Grade 3) and 16.0% (4.0% Grade 3) of participants in Cohorts 1a and 1b, and 5.2% (0.5% Grade 3) of participants in Cohort 3, and were mostly mild or moderate, and resolved within 1 to 2 days after vaccination. The most frequent solicited local adverse event was injection site pain and the most frequent solicited systemic adverse events were fatigue, headache and myalgia. The safety and reactogenicity profiles of 2 dose levels, 5×10^{10} and 1×10^{11} vp were considered acceptable. No data are available in children.

For the most comprehensive nonclinical and clinical information regarding Ad26.COV2.S, refer to the latest version of the IB (IB Ad26.COV2.S 2022).

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), has been observed very rarely following vaccination with Ad26.COV2.S. These cases occurred approximately 1-2 weeks following vaccination, mostly in adult women (CDC 2021b). Even though thrombosis in combination with thrombocytopenia can be fatal, the exact physiology of TTS is unclear. TTS is considered a post-vaccination risk for Ad26.COV2.S vaccine. Participants will be asked daily if they have experienced any health concerns (including new onset of symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches or blurred vision, easy bruising, or tiny blood spots under the skin beyond the site of the injection) within the 30-day time period post-vaccination, and if so, participants will be advised to contact the study center. 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, ASH 2021; BSH 2021; CDC 2021a). 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.

The sponsor's own independent benefit-risk assessment in children younger than 18 years of age, demonstrated that the key benefits of vaccinating with the Ad26.COV2.S vaccine (ie, protection against the risk of COVID-19 related deaths, COVID-19 related hospitalizations, Multisystemic Inflammatory syndrome in Children [MIS-C], and deaths due to MIS-C [CDC 2020k]) greatly outweighed the potential key risk of thrombosis with thrombocytopenia.

Reports of adverse events following use of the Ad26.COV2.S vaccine under emergency use authorization (EUA) suggested an increased risk of Guillain-Barré syndrome (GBS) during the 42 days following vaccination. Investigators should be alert to GBS signs and symptoms to facilitate

diagnosis, to initiate adequate supportive care and treatment, and to rule out other causes. Refer to the latest version of the IB and its addenda (if applicable) for further details.

Risks Related to a 3rd vaccination with Ad26.COV2.S

In an interim analysis of study COV1001 (cut-off 21 Jul 2021) in which 15 participants (>18 years of age) received 3 doses of Ad26.COV2.S at the 5×10^{10} vp dose level (Month 0, 2, and 8) and 46 participants received 2 doses of Ad26.COV2.S at the 5×10^{10} vp dose level at Month 0 and 2, followed by placebo at Month 8, no safety concerns were identified. Lower frequencies of solicited systemic AEs and unsolicited AEs were observed post-dose 3 compared to post-dose 1.

In an interim analysis of study COV2001 (cut-off 11 May 2021) in which 264 participants (which included 33 adolescents) received 3 doses of Ad26.COV2.S (first 2 doses at 1.25×10^{10}, 2.5×10^{10}, or 5×10^{10} vp dose level, 3rd dose [antigen presentation] at 1.25×10^{10} vp dose level) and 44 participants received placebo, reactogenicity post-antigen presentation (3rd dose) was generally similar with no sign of increase compared to post-dose 1.

Risks Related to Adenoviral-vectored Vaccines

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

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

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

The most frequently experienced solicited local AE in children was injection site pain, reported in 13.9% of children aged 1 to 3 years, 29.8% of children aged 4 to 11 years, and 24.8% of children aged 12 to 17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4 to 11 years and 14.3% in adolescents aged 12 to 17 years. No children aged 1 to 3 years have received placebo.

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

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

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

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

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

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

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

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

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue in adults and children ≥6 to <12 years of age and fever, loss of appetite, diarrhea, vomiting, decreased activity, lethargy, irritability, and crying in children <6 years of age. These side effects will be monitored but are generally short-term. Instructions regarding use of antipyretic medication can be found in Section 6.7.

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, vomiting, breath-holding, and rarely to seizures.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria, or even anaphylaxis, severe reactions are rare (IB Ad26.COV2.S 2022). Participants with a known or suspected allergy or history of anaphylaxis, or other serious adverse reactions, related to vaccines or their excipients (including specifically the excipients of the study vaccine) will be excluded from the study.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for the Dose Selection Cohort (or longer if required by institutional/local practice) and will be closely observed by study site staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

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

Capillary Leak Syndrome

Capillary leak syndrome (CLS) is a rare disease that causes edema, hypoproteinemia, episodic hypotension, dyspnea, hyponatremia, and weight gain that can be life-threatening. Although the underlying pathology is currently unknown, CLS is thought to be secondary to disruption of the endothelium and generalized edema. No cases of CLS have been reported in Ad26.COV2.S vaccine studies. Individuals with a history of CLS will be excluded from participating in this study (Section 5.2; Exclusion Criterion 24) and CLS is a contraindication for administering a second dose of the study vaccine (Section 7.1).

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.

Participants of childbearing potential will be required to agree to practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent or assent until 3 months after receiving study vaccine (see Section 5.1). Participants who are pregnant or breastfeeding will be excluded from the study. Participants who become pregnant during the study will not receive further study vaccine but should continue to undergo all procedures for surveillance and follow-up of COVID-19 and all safety follow-up as outlined in the protocol for all participants.

Risks from Blood Draws

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

Risks from Collection of Nasal Swab Samples

Collection of a nasal swab sample may cause a nosebleed.

Theoretical Risk of Enhanced Disease

VAERD has been described for SARS-CoV and MERS-CoV in some animal models (Agrawal 2016; Bolles 2011; Deming 2006; Honda-okubo 2015; Houser 2017), and is associated with non-neutralizing antibodies and a Th2-skewed immune response, but proof of human SARS-CoV or MERS-CoV VAERD does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. 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). The initial clinical immunogenicity data from Study COV1001 have also demonstrated the induction of a Th1-skewed response in all participants in both Ad26.COV2.S vaccine dose groups, indicating that the theoretical risk for predisposition of VAERD is minimal, also in case antibodies are transferred to the infant via the placenta (IB Ad26.COV2.S 2022). Participants in the present study will be informed of the theoretical risk of disease enhancement in the ICF/assent form. Furthermore, as a risk mitigation strategy, adolescents in the study will be monitored for acquisition of molecularly confirmed COVID-19 (see Section 4.1, Section 8.1.2, and Section 10.9). This 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. In addition, selected members of the Statistical Support Group (SSG), not otherwise involved in the study, will receive individual level unblinded data pertaining to Study COV3006 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. The SSG will immediately inform the IDMC as soon as an imbalance between groups is detected. A prespecified threshold (imbalance above a certain percentage and/or number of cases) that will trigger notification of the IDMC will be described in the 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 in pediatric population have yet to be established. Currently, there is only limited availability of authorized vaccines for the prevention of COVID-19 in the pediatric population. No efficacy can be concluded yet from current data on Ad26.COV2.S. The overall benefit and risk balance for individual participants thus cannot be ascertained. Participants must be informed that this vaccine has not yet been proven to be effective, and it should be assumed that it is not the case until clinical studies are conducted to demonstrate its effectiveness.

2.3.3 Benefit-Risk Assessment of Study Participation

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

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

  In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Schedule of Activities (Section 1.3).

After each vaccination, participants will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) and will be closely observed by study site staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a reactogenicity diary in the eCOA to document solicited signs and symptoms. Details are provided in Section 8.3.

The investigator or the designee will document unsolicited AEs, SAEs and MAAEs as indicated in Section 8.3 and Section 10.4.

From the time of local approval of protocol Amendment 1 onwards, TTS is considered to be an AESI (Section 8.3.6.1). Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/µL] [BC 2021]) 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 1.3.4.1.

From the time of local approval of protocol Amendment 1 onwards, MIS-C is considered to be an AESI (Section 8.3.6.2). Suspected AESIs 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 1.3.4.2.

Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until clinically stable.

An IDMC will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. This committee will review unblinded data. The IDMC will also review Day 29 and Day 85 safety data at specific occasions during the sequential enrollment of adolescents, as described in Section 4.1. Additional ad hoc reviews may be performed further to the occurrence of any SAE leading to a study pausing situation as outlined in Section 6.8, or at request of the sponsor's medical monitor or designee. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:

  Eligibility will be reassessed pre-vaccination at the day of the first vaccination.

  The study will start enrollment of the different age groups (16 to 17 years of age and 12 to 15 years of age) simultaneously. Enrollment will begin with the recruitment of participants to a Dose Selection Cohort in both the 1- and 2-dose regimen. Both the 1- and 2-dose regimen will start simultaneously. If it is deemed more appropriate to continue with a lower dose level than either 2.5×10^{10} vp or a 1.25×10^{10} vp dose level, then the use of these doses may be considered and removed in a future protocol amendment.

  Adolescents will be monitored in this study to rapidly diagnose COVID-19 and refer for treatment, if applicable. This will mitigate the theoretical potential risk for VAERD when immunized individuals are infected with the virus. The observed induction of neutralizing antibodies and Th1-skewed response by this vaccine in Study COV1001 indicate that the theoretical risk for predisposition of VAERD is minimal.

There are prespecified rules for all participants, that if met would result in pausing of further vaccinations (see Section 6.8), preventing exposure of new participants to study vaccine until the IDMC reviews all safety data (see Section 10.3.6).

Study vaccinations will be discontinued in participants for the reasons included in Section 7.

Contraindications to vaccination are included in Section 5.5.

3. OBJECTIVES AND ENDPOINTS

Part 1 Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of Ad26.COV2.S administered intramuscularly (IM) as a 1-dose regimen (at 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level) or as a 2-dose (56-day interval) regimen (2.5×10^{10} vp per 0.5 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) in adolescents.	• Solicited local and systemic adverse events (AEs) for 7 days post-dose 1 and 2. • Unsolicited AEs for 28 days post-dose 1 and 2. • Medically-attended adverse events (MAAEs) from the first vaccination until 6 months post-dose 1 or post-dose 2. MAAEs leading to discontinuation will be collected during the entire study. • Serious adverse events (SAEs) from the first vaccination until the end of the study. • Adverse events of special interest (AESI) from first vaccination until end of the study (incl. MIS-C).
• To assess the humoral immune response of Ad26.COV2.S administered IM as a 1-dose regimen (at 2.5×10^{10} vp per 0.25 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose level) or as a 2-dose (56-day interval) regimen (2.5×10^{10} vp per 0.5 mL, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) in adolescents.	• Serological response to vaccination as measured by spike-enzyme-linked immunosorbent assay (S-ELISA) (ELISA; Units/mL [EU/mL]) or equivalent assay, or virus neutralization assay (VNA) titers at 28 days post-dose 1 and 14 days post-dose 2.

Part 1 Secondary and Exploratory Objectives and Endpoints

Secondary	
• To assess the humoral immune response to 3 dose levels of Ad26.COV2.S (2.5×10^{10} vp, 1.25×10^{10} vp, or 0.625×10^{10} vp) and regimens in all study groups, at all blood collection timepoints.	• Serological response to vaccination measured by binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA (or equivalent assay), and/or • Serological response to vaccination measured by neutralizing antibody titers to SARS-CoV-2 (VNA).
• To assess the safety and reactogenicity of Ad26.COV2.S administered IM as a booster in adolescent participants (Groups 1-3).	• Solicited local and systemic AEs for 7 days post-booster. • Unsolicited AEs for 28 days post-booster. • MAAEs from the booster until 6 months post-vaccination.
• To evaluate the humoral immune response in adolescent participants who receive a booster dose during the study, pre-boost and at selected time points post booster vaccination (Groups 1-3).	• Serological response to vaccination measured by binding (S-ELISA and/or equivalent assay) and/or neutralizing (VNA) antibody titers
Exploratory	
• To examine the immune response in vaccinated adolescents after 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. • SARS-CoV-2-binding antibodies measured by ELISA (or equivalent assay): Analysis of antibodies binding to the SARS-CoV-2 S and/or N protein. • Analysis of gene expression by RNA transcript profiling in adolescents 12 to 17 years of age.
• To assess the correlation between the binding antibodies (S-ELISA) and neutralizing antibody (VNA) titers to SARS-CoV-2 at selected timepoints.	• Correlation between binding antibodies (S-ELISA; EU/mL, or equivalent assay) and VNA (wtVNA and/or psVNA) titers at selected timepoints.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms in adolescents.	• The number of adolescents with molecularly confirmed COVID-19. • Presence and severity of COVID-19 signs and symptoms as measured by the Symptoms of Infection with Coronavirus-19 (SIC).
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• Serologic conversion between baseline (Day 1; pre-vaccination) and selected timepoints post-vaccination using an ELISA and/or SARS-CoV-

	2 immunoglobulin assay that is dependent on the SARS-CoV-2 N protein • The number of asymptomatic participants with a SARS-CoV-2 positive molecular test. • *For asymptomatic case definition, see Section 10.9.3.*
• To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.	• Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA or equivalent assay.
• To assess the impact of the Ad26.COV2.S vaccine on the incidence of co-infections with SARS-CoV-2 and other respiratory pathogens in adolescents who have received Ad26.COV2.S during the study.	• Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in nasal swab samples from adolescents with a symptomatic infection.
• To assess the presence of SARS-CoV-2 variants during a confirmed COVID-19 episode in adolescents. • To assess SARS-CoV-2 viral load during a confirmed COVID-19 episode in adolescents.	• Identification of SARS-CoV-2 variants by sequencing of nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode. • Analysis of SARS-CoV-2 viral load (via qRT-PCR) in nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode.
• To further explore the humoral immune responses in participants who have received Ad26.COV2.S.	Exploratory analyses may include the following assays: • SARS-CoV-2 neutralization as assessed by VNA. • Adenovirus neutralization as measured by VNA. • Analysis of neutralizing and binding antibodies against emerging SARS-CoV-2 virus lineages. • Functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass and IgG isotype, antibody glycosylation, and assessment of antibody repertoire. • Analysis of antibodies to S, N, and the receptor binding domain (RBD) of the SARS-CoV-2 S protein, and surface proteins of other coronaviruses. • Epitope-specificity characterization of antibodies. • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or

	adaptive immune response in the serum or plasma. • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. • Seroresponse rates according to different responder definitions.

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 be performed in addition, as outlined in a revised SAP.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

No formal hypothesis testing is planned in Part 1. Descriptive statistics will be used to compare vaccine immunogenicity in adolescents from study VAC31518COV3006 versus vaccine immunogenicity in young adults (18 to 25 years of age) from study VAC31518COV3001 or VAC31518COV3009 and between study groups in VAC31518COV3006. Descriptive statistics will be used to summarize the safety and reactogenicity endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, observer-blind, pivotal Phase 2 study in healthy adolescents from 12 to 17 years of age. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S in a 1- and 2-dose (56-day interval) vaccination regimen will be evaluated. The study will descriptively compare the immune responses measured by S-ELISA (and potentially VNA) in adolescents versus the immune responses measured in young adults (18 to 25 years of age) from study VAC31518COV3001 (after administration of 1 dose of Ad26.COV2.S) or VAC31518COV3009 (after administration of 2 doses of Ad26.COV2.S) and between study groups in VAC31518COV3006. This study consists of a Dose Selection Cohort (Table 2).

Previously, this study was designed to comprise Part 1 and Part 2, wherein Part 2 included the Extension Cohort of vaccine naïve participants for evaluation of the dose level and dose regimen selected after review of the data in Part 1. Per protocol amendment 4, Part 2 will no longer be conducted

Participants will receive Ad26.COV2.S as a first dose and Ad26.COV2.S or placebo as a second dose. Ad26.COV2.S will be administered IM at 1 of up to 3 dose levels: 2.5×10^{10} vp, 1.25×10^{10} vp, or 0.625×10^{10} vp.

A target of approximately 300 adolescents seronegative for SARS-CoV-2 antibodies at baseline (as assessed by local serology finger-prick testing) will be enrolled in a 2-dose vaccination regimen

with 1 or 2 active vaccinations, with placebo administered as a second dose for those in the 1-dose regimen.

Participants in a Dose Selection Cohort will be randomly assigned in a 1:1:1:1:1:1 ratio to 1 of 6 study arms: a) to receive one active vaccination of Ad26.COV.2 (either 2.5×10^{10} vp per 0.25 mL dose volume, 1.25×10^{10} vp, or 0.625×10^{10} vp) followed by placebo at Day 57 in a 1-dose regimen (Groups 1, 2, and 3, respectively), or b) to receive 2 active vaccinations of the same dose level (either 2.5×10^{10} vp per 0.5 mL dose volume, 1.25×10^{10} vp, or 0.625×10^{10} vp) in a 2-dose (56-day interval) regimen (Groups 4, 5, and 6, respectively). Each group will contain 50 participants, of which approximately 70% need to be 12 to 15 years of age and approximately 30% need to be 16 to 17 years of age to limit unnecessary exposure in case of safety concerns (including specific pausing rules, see Section 6.8). Adolescents will be unblinded to the primary vaccination regimen at 6 months after the first vaccination.

Participants in Groups 1-3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine (Vaccination 1). The booster dose level for all participants in Groups 1-3 will be 2.5×10^{10} vp per 0.5 mL.

Participants in Groups 4-6 will not be administered a booster vaccination, given they will receive 2 active vaccinations in the primary vaccination regimen.

As a part of the COVID-19 program safety oversight, the IDMC will review the data on an ongoing basis, in addition to two study-specific predefined IDMC analyses. A first IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 1. A second IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 2. Selected sponsor members will review group unblinded summaries of those data, as well as any available immunogenicity data up to 28 days post-dose 1 and 14 days post-dose 2. Based on the review, the sponsor will select the dose level for any future pediatric studies based on the safety and reactogenicity data (28 days after each vaccination) and any available immunogenicity data (28 days post-dose 1 for the 1-dose regimen, and 14 days post-dose 2 for the 2-dose regimen). Non-binding guidelines on dose and regimen selection will be described in the SAP. Decision making on the optimal dose and regimen may take into account safety, reactogenicity and immunogenicity data from other Ad26.COV2.S clinical studies (such as that of young adults in study VAC31518COV3001 and study VAC31518COV3009 and adolescents from study VAC31518COV2001).

The randomization will take into account having not more than 70% males or females in each age group, as evenly divided as possible over the different age groups. Stratification is by sex and age group. Screening will aim to ensure participants are seronegative for SARS-CoV-2 antibodies at baseline by utilizing the finger-prick test (by testing blood from a small puncture in the finger).

Table 2: Part 1 Vaccination Schedules (Dose Selection Cohort)

Group	N[a,b,c]	Vac 1 Day 1	Vac 2 Day 57	Vac 3[d] Day 184
1	50	2.5×10^{10} vp (0.25 mL)	Placebo	2.5×10^{10} vp (0.5 mL)
2	50	1.25×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
3	50	0.625×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
4	50	2.5×10^{10} vp (0.5 mL)	2.5×10^{10} vp (0.5 mL)	
5	50	1.25×10^{10} vp	1.25×10^{10} vp	
6	50	0.625×10^{10} vp	0.625×10^{10} vp	

N number of participants; Vac vaccination; vp virus particles.

a Not more than 70% of males or females should be randomized in each age group.

b All participants must be seronegative for SARS CoV 2 antibodies at baseline (by finger prick test).

c Approximately 30% of participants should be between 16 to 17 years age and approximately 70% should be between 12 to 15 years of age.

d Participants in Groups 1 3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine (Vaccination 1) and the booster dose level for these participants will be 2.5×10^{10} vp per 0.5 mL.

Study Duration

The study duration from screening until the last follow-up visit will be, excluding the 28-day screening phase, approximately 8 months (Groups 4-6) to12 months (Groups 1-3) provided the intervals in the SoA are respected, consisting of:

- Groups 1-3: ~12-month study duration comprising a 6-month study period including vaccination with 1 active dose and a placebo vaccination (56-day interval), followed by a booster vaccination at 6 months and follow-up (safety and immunogenicity) until at least 6 months after booster vaccination.
- Groups 4-6: ~8-month study duration comprising 2 active doses (56-day interval) and follow-up (safety and immunogenicity) until at least 6 months after second vaccination.

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, MAAEs, SAEs, and AESIs. Other safety assessments include vital signs measurements (heart rate, preferably supine systolic and diastolic blood pressure, respiratory rate, and body temperature) and physical examinations at the time points indicated in Section 1.3, Schedule of Activities.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) for presence of any acute reactions and solicited events. Any solicited local or systemic AEs, unsolicited AEs, SAEs, AESIs, 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 post-vaccination observation period is complete. In addition, participants will record solicited signs and symptoms in a reactogenicity diary for 7 days post-vaccination.

The reporting periods of AEs, MAAEs, SAEs, AESIs, and special reporting situations are detailed in Section 8.3. Reporting periods for concomitant therapy are outlined in Section 6.7.

A final safety follow-up visit is foreseen 6 months after the last active vaccination.

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

At the time of study entry, participants or parent(s)/caregiver(s) will need to indicate to the site staff, in case they, or their child, respectively would get infected with SARS-CoV-2, and contact details of a local physician and/or facility where they would obtain emergency care and hospitalization for the participant, if necessary. If a participant should have COVID-19 and their symptoms deteriorate, participants or parent(s)/caregiver(s) will be recommended to go to the HCP or hospital that has been identified in advance. For the duration of the study, the participant will be asked, through the eCOA, if they have experienced any new symptoms or health concerns that may require seeking emergency care.

All adolescents with COVID-19-like signs or symptoms and adolescents with a positive RT-PCR test from outside the study meeting the prespecified criteria for suspected COVID-19[a] should undertake the COVID-19 procedures until 14 days after signs or symptom onset/positive RT-PCR test from outside the study (COVID-19 Day 15) or until resolution of the COVID-19 episode, whichever comes last, unless it is confirmed that the COVID-19 Day 1 to 3 nasal swab (for those that have it) is negative for SARS-CoV-2. Resolution of the COVID-19 episode is defined as having 1 SARS-CoV-2 negative nasal swab and 2 consecutive days with no COVID-19-related signs or symptoms. The procedures in case of (suspected) COVID-19 are detailed in Section 8.1.2.1. At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition (see Section 10.9).

All necessary precautions (per local regulation) should be taken to protect medical staff and other contacts of adolescents who are suspected to have COVID-19 or have a positive molecular test from inside the study or RT-PCR test from outside the study for SARS-CoV-2. In the event of a confirmed SARS-CoV-2 infection, participant's medical care provider will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations. Site staff and participants will not be blinded as to the outcome of the molecular test results from the local (hospital) laboratory. Their routine HCP can obtain external diagnostics,

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

including molecular diagnostic RT-PCR or other molecularly confirmed viral tests, as medically needed.

The occurrence of asymptomatic SARS-CoV-2 infection will be assessed in adolescents by a non-S protein ELISA and/or SARS-CoV-2 immunoglobulin assay (eg, SARS-CoV-2 N-ELISA) (see Section 8.1.5) and by collection of any positive molecular results 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).

From all participants, blood samples will be collected at selected timepoints for humoral immunogenicity assessments, with an emphasis on binding and neutralizing antibody responses. Additional blood samples for humoral immunogenicity assessments will be taken in case of a COVID-19 episode. Blood sampling timepoints are indicated in the SoA in Section 1.3, and further details about the immunogenicity assessments are provided in Section 8.1.1.

An IDMC will be commissioned for this study, committee membership responsibilities, authorities, and procedures will be documented in its charter. Refer to Committees Structure in Section 10.3.6.

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

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

4.2. Scientific Rationale for Study Design

Dose Selection

The rationale behind the selection of the 3 dose levels is described in Section 4.3.

Blinding, Control, Study Phase/Periods, Intervention Groups

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

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

Biomarker Collection

For adolescents with a positive molecular test result for SARS-CoV-2 infection, biomarker analysis (PAXgene®, RNA-seq) may 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 guardian 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 guardian 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 adolescents whose benefit from participation in the study is unknown.

The potential risks to 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. See Section 2.3 for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

Participants will be monitored for AEs throughout the study, and an IDMC will be established as described in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

Before the performance of any study-related assessments, written informed consent and assent (if applicable) must be obtained following the process described under Informed Consent Process and Assent Form in Section 10.3.3.

When referring to the signing of the informed consent/assent form (ICF), the terms legal guardian and legally acceptable representative refer to the legally appointed guardian(s) of the adolescent with authority to authorize participation in research. For each adolescent 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 must be obtained from adolescents (minors) capable of understanding the nature of the study depending on the institutional policies and local regulations. 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 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 parent(s) or legal guardian still want them to participate.

The total blood volume to be collected in adolescents is considered to be an acceptable amount of blood to be collected over this time period from the population in this study (US FDA 1998;

US DHHS 1998; EU 2008; EMA 2017; Howie 2011; Peplow 2019; Veal 2014). The total blood volume to be collected at a single time will not exceed approximately 28.5 mL per blood draw for adolescents 12 to 17 years of age.

4.3. Justification for Dose

The regimen and dose selection in this study are aimed at providing information on safety, reactogenicity, and immunogenicity of 1- and 2-dose schedules of Ad26.COV2.S at 3 dose levels (2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp) in adolescents. Available platform data, as well as safety data from the VAC31518COV1001 and VAC31518COV2001 studies, (see Section 2.2 and Section 2.3.1) support initiating evaluation of Ad26.COV2.S in the pediatric population, at the dose levels 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp.

In this study, 3 dose levels of Ad26.COV2.S will be evaluated: 2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp.

- The 2.5×10^{10} vp dose level is currently being evaluated in the VAC31518COV2001 study. In COV2001, Ad26.COV2.S is being evaluated at a range of doses and intervals (1.25×10^{10} vp, 2.5×10^{10} vp, 5×10^{10} vp, and 1×10^{11} vp) in adolescents 12 to 17 years of age, adults 18 to 55 years of age and 65 years of age and above. This lower 2.5×10^{10} vp dose is being evaluated since the Ad26-based Ebola vaccine demonstrated higher immune response in younger age groups. Therefore, a 2.5×10^{10} vp dose level in adolescents might elicit a similar response when compared with a 5×10^{10} vp dose level in adults.

Details about dose modification during the study are described in Section 6.5.

4.4. End of Study Definition

End of Study Definition

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

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at the 6-month post last active vaccination visit. Note that, in case participants do not receive a booster vaccination in Groups 1-3, they will nevertheless be considered to have completed the study provided they have completed a 6-month follow-up post active vaccination.

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 these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

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 vaccine is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria is described in Section 10.3.10.

5.1. Inclusion Criteria

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

1 Criterion modified per Amendment 1:

1.1 Criterion modified per Amendment 3

1.2 Each participant and/or participant's parent(s)/legal guardian(s) must sign an ICF according to local regulations, indicating that they understand the purpose of, and procedures required for the study, are willing to participate or for their child to participate in the study and attend all scheduled visits, and are willing and able to adhere to the prohibitions and restrictions specified in the protocol and study procedures, including maintaining contact with the site until 6 months after the last vaccination. Participants will be asked to give positive assent per local practices and regulations.

Note: For each participant, at least one parent or legal guardian, if applicable according to local regulations, must give written consent. In countries where regulation requires that both parents/legal guardians give consent, this will be applicable.

2 Participant has given written assent as required by local regulations after the nature of the study has been explained to them according to local regulatory requirements.

3 Criterion modified per Amendment 1:

3.1 Participant's age is 12 to 17 years of age at the time of first vaccination.

4 Criterion removed by Amendment 1

5 Participant must be healthy, in the investigator's clinical judgement, 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.

6 Contraceptive (birth control) use by a participant of childbearing potential 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 10.6, Contraceptive Guidance):

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/ligation procedure

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

6. sexual abstinence*

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and 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 on the day of and 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 counselling and follow-up will be made available.

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 and/or parent(s)/legal guardian(s) are available and willing to participate for the duration of the study visits and follow-up.

10 Participant and/or 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.

11 Each participant or participant's parent(s)/legal guardian(s) must have access to a consistent means of contact either by telephone contact or email/computer.

12 Criterion modified per Amendment 1:

12.1 Participant must be able to read, understand, and complete questionnaires in the eCOA (ie, the COVID-19 signs and symptoms surveillance question, the SIC as a PRO, and the reactogenicity diary).

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

5.2. Exclusion Criteria

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

1 Participant has a clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned first dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.

2 Participant has a history of malignancy, bone marrow transplant, or solid organ transplant within 5 years before screening.

3 Participant has a known or suspected allergy, history of anaphylaxis, or other serious adverse reactions, related to vaccines or their excipients (including specifically the excipients of the study vaccine) (refer to the IB Ad26.COV2.S 2022).

4 Use of systemic corticosteroids at an immunosuppressive dose (treatment duration more than 14 days for one course or recurrent use) within 6 months before administration of study vaccine and during the study

Note: For corticosteroids, this means prednisone, or equivalent, ≥20 mg/day. For participants below 45 kg, the dose is above 1 mg/kg/day.

Ocular, topical, or inhaled steroids are allowed.

Non-immunomodulator treatment is allowed as well as steroids at a physiologic dose.

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 Criterion modified per Amendment 1:

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

Note: Stable and medically well controlled chronic conditions (defined as no change in medication over the past 6 months, other than weight-based adjustments for normal growth) are allowed per investigator discretion such as:

- Diabetes: $HgbA_{1c}$ <7% and/or no episodes of diabetic ketoacidosis in the past 6 months.
- Cardiac disease (eg, arrhythmias, heart murmurs): Repaired cardiac defects without residual lesions. No surgery or intervention (eg, trans catheter procedures) in the past 6 months and no anticipated procedures for 6 months post first vaccination.
- Blood dyscrasias: (eg, thalassemia) with no blood transfusions in the 4 months before the planned administration of the first dose of study vaccine.
- Autoimmune disease not requiring immune-modifying or steroid treatment.
- HIV.
    a. CD4 cell count ≥500 cells/mm^3
    b. HIV viral load <50 copies/mL
    c. Participant must be on a stable anti-retroviral treatment (ART) for 6 months (unless the change is due to tolerability, in which case the regimen can be for only the previous 3 months; changes in formulation are allowed) and the participant must be willing to continue his/her ART throughout the study as directed by his/her local physician.

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

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

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

7 Participant has extreme obesity (body mass index [BMI] ≥35 or as defined by the Growth Chart being used as appropriate in the participant's country, eg, the CDC Growth Chart [CDC 2020i]).

8 Criterion modified per Amendment 1:

8.1 Participant has a history of chronic dermatologic conditions such as urticaria (recurrent hives), eczema or atopic dermatitis.

9 Participant has a known history of Kawasaki disease.

10 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.

11 Criterion modified per Amendment 1:

11.1 Participant received or plans to receive:

a. Licensed live attenuated vaccines within 28 days before or after planned administration of a study vaccination (14 days before and after for rotavirus vaccine in adolescents).

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

12 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 immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months, or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the 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 18) and during the study.

13 Participant is pregnant.

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

15 Participant is a family member 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, or a known family member of the sponsor.

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

17 Participant or participant's parent(s)/legal guardian who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study or participant who is unlikely to complete the full course of vaccination and observation.

18 Participant previously received a coronavirus vaccine.

19 History of confirmed SARS or MERS.

20 Criterion removed per Amendment 1

21 An adolescent of a parent/legal guardian not capable of understanding the key aspects of the study and their requirements for participation (only applicable if parent[s]/legal guardian must sign the ICF according to local regulations).

22 Participant's parent(s)/legal guardian is <18 years of age and not of legal age according to local regulations.

23 Criterion added per Amendment 1

23.1 For Part 1 only: Participant has a positive diagnostic test result for past (serological testing) SARS-CoV-2 infection at screening.

24 Criterion added per Amendment 1

24.1 History of CLS.

25 Criterion added per Amendment 1

25.1 A participant that is on medication that may lead to risk of blood dyscrasias or thrombotic events.

26 Criterion added per Amendment 1

26.1 A participant has a history of any serious, chronic, or progressive neurological disorders or seizures including Guillain-Barré syndrome, with the exception of febrile seizures during childhood.

27 Criterion added per Amendment 2

27.1 History of Heparin-induced thrombocytopenia

5.3. Lifestyle Considerations

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

1 Refer to Section 6.7 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 (Section 5.1 and 5.2).

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. 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/assent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent/assent will be used.

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

Participants who were screened and randomized to the Placebo arm for Part 1 under Protocol Amendment 1, will be given the option to rescreen and enroll in one of the active arms under Protocol Amendment 2.

5.5. Criteria for Temporarily Delaying Administration of Study Vaccine

The following events assessed by the investigator 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. All participants may be rescreened once (see Section 5.4). 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).

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 VACCINE(S) AND CONCOMITANT THERAPY

6.1. Study Vaccine(s) Administered

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

Participants allocated to the 2.5×10^{10} vp dose level will receive 1 of 2 volumes: 0.5 or 0.25 mL. A volume of 0.5 mL will be administered to participants in all other dose groups.

Participants will be vaccinated at the study site according to the schedules detailed in Section 4.1. 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. Alternating injection sites will be used for all study vaccinations unless there is a medically justifiable reason in the judgement of the investigator.

For information on vaccination windows, see Section 8. If a participant cannot be vaccinated within the allowed window (eg, if the window is missed due to a study pause [see Section 6.8]), the decision regarding vaccination will be assessed on a case-by-case basis, upon discussion between sponsor and investigator.

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 (IB Ad26.COV2.S 2022) for a list of excipients.

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

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

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

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

Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be

documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study vaccine containers.

Study vaccine must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's unblinded 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 has 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 for adolescents 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. The randomization will be balanced by using randomly permuted blocks and will be stratified by age group (adolescents 16 to 17 years and 12 to 15 years), and sex (boys and girls). The participants in the Dose Selection Cohort (Table 2) will be randomly assigned in a 1:1:1:1:1:1 ratio to 1 of 3 cohorts to receive Ad26.COV.2 (either 2.5×10^{10} vp per 0.25 mL dose volume, 1.25×10^{10} vp, or 0.625×10^{10} vp) followed by placebo in a 1-dose regimen, or 1 of 3 cohorts to receive the same dose level of 2.5×10^{10} vp per 0.5 mL dose volume, 1.25×10^{10} vp or 0.625×10^{10} vp, in a 2-dose (56-day interval) regimen. The randomization will take into account having not more than 70% of males or females in each age group, as evenly divided as possible over the different groups.

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

Blinding

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 unblinded study vaccine administrator. Adolescents will be randomly assigned to 1 of the groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor and using the IWRS.

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

Data that may potentially unblind the vaccine assignment (ie, immunogenicity data, study vaccine accountability data, study vaccine allocation, biomarker, vaccine/dose volume) 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.

The sponsor will be unblinded at the time of primary analysis. Note that for potential interim analyses before the primary analysis, unblinded data at the vaccination group level may be available for sponsor personnel involved and an independent SSG will receive individual level unblinded data, when unblinding at the participant level is required. Table 3 Details will be provided in the IDMC Charter. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, the investigator should attempt to discuss with the sponsor or representative prior to breaking the blind. Telephone contact of the sponsor will be made available. 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 eCRF. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded prior to the scheduled unblinding timepoint, 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 locked. 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.

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 upon written communication form the sponsor. 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 in the eCRF. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see Section 6.7).

If it is determined that the participant received the SARS-CoV-2 vaccine upon unblinding, the participant will be informed that there are no data on the safety of receiving one of 3 different doses of COVID-19 vaccines. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the SoA to the extent that they permit. Safety, efficacy, and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding for safety, efficacy, and immunogenicity, as described in the SAP.

6.4. Study Vaccination Compliance

Study vaccines will be administered IM by a unblinded qualified study vaccine administrator a trained and qualified study nurse, medical doctor, or otherwise qualified HCP at the study site. For blinding procedures, see Section 6.3. The date and time of study vaccine administration and the location of injection will be recorded in the eCRF.

6.5. Dose Modification

The safety, reactogenicity and available immunogenicity data of participants in the Dose Selection Cohort (2.5×10^{10} vp, 1.25×10^{10} vp, and 0.625×10^{10} vp dose levels) will be reviewed by the IDMC (see Section 4.1). The lowest dose level (and any/all lower dose levels) that is deemed to produce acceptable reactogenicity, provided it induces adequate immunogenicity, as identified during this review, will be considered for future development.

6.6. 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/MAAEs: the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reactions by site 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.

6.7. Prestudy and Concomitant Therapy

Prestudy 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, but not limited to, analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the moment of first vaccination until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of any subsequent vaccination and for 28 days after that vaccination. 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. Concomitant therapies associated with an SAE meeting the criteria outlined in Section 10.4.1 will be collected and recorded in the eCRF from the moment of first vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF from the moment of first vaccination through the end of the study.

Use of any experimental medication (including experimental vaccines other than the study vaccine) will lead to discontinuation of administration of any subsequent 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 investigational or other immunoglobulin 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. During the study, the use of investigational vaccines other than the study vaccine is not allowed, and the use of investigational drugs is only allowed if medically indicated. Treatment with investigational COVID-19 drugs after diagnosis of a COVID-19 case is allowed during the follow-up period and needs to be recorded in the COVID-19 episode description.

Licensed live attenuated vaccines should be given at least 28 days before or at least 28 days after a study vaccination (14 days before and after for rotavirus vaccine in adolescents) and must be recorded. Other licensed (not live) vaccines (eg, the DTaP [reduced Diphtheria toxoid, Tetanus toxoid, and acellular Pertussis], influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before or at least 14 days after a study vaccination in order to avoid potential confusion of adverse reactions and potential immune interference and must be recorded.

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 and should

be discussed with the sponsor to determine if continued study vaccination is feasible, and any vaccinations must be recorded. Adolescents receiving routine immunizations according to their local vaccination schedules (eg, in Europe, the applicable national immunization schedules, and the equivalent in other countries) should not be postponed due to study participation and all vaccinations must be recorded.

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 only in special circumstances.

Chronic (>14 days) or recurrent use of systemic corticosteroids[a], at immunosuppressive doses and administration of antineoplastic and immunomodulating agents or radiotherapy are prohibited during the study and within 6 months before the planned administration of the first dose of study vaccine. If any of these agents are indicated in a disease setting, these must take priority over the study vaccine.

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

The sponsor must be promptly notified 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, a participant who receives a prohibited concomitant medication will not be included in the immunogenicity analyses.

6.8. Study Vaccination Pausing Rules

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

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

After the first IDMC meeting triggered by the occurrence of a given pausing rule, the IDMC 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 (once the pause is lifted, the decision regarding subsequent vaccination [if applicable] will be

[a] Note: Ocular, topical, or inhaled steroids are allowed. Non-immunomodulator treatment is allowed as well as steroids at a physiologic dose.

assessed on a case by-case basis, upon discussion between sponsor and investigator). 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 to IDMC for information. Upon their review, IDMC 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. One or more participants experience MIS-C which is assessed as at least possibly related to study vaccine; OR
5. Three participants from the Dose Selection Cohort (of the same dose level group, within the same age group, and from the same 2 dose vaccination regimen with 1 or 2 active vaccinations, with placebo administered as a second dose for those in the 1-dose regimen) experience a Grade 3 unsolicited AE of the same type (per medical judgement of the sponsor), that is determined to be related to study vaccine; OR
6. Three participants from the Dose Selection Cohort (of the same dose level group, within the same age group, and from the same 2 dose vaccination regimen (56-day interval) with 1 or 2 active vaccinations, with placebo administered as a second dose for those in the 1-dose regimen) experience a persistent (upon repeat testing) Grade 3 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine; OR
7. Three participants from the Dose Selection Cohort (of the same dose level group, within the same age group, and from the same 2 dose vaccination regimen (56-day interval) with 1 or 2 active vaccinations, with placebo administered as a second dose for those in the 1-dose regimen) 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).
8. One or more cases of suspected TTS, possibly related to the vaccine.

For number 2 and number 6: 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 5, number 6, and number 7: after each IDMC review of similar AE, the committee will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

Note: the occurrence of a study pause in any other ongoing study with Ad26.COV2.S may trigger a study pause in further vaccination in the current study, if considered to be medically relevant. Any subsequent delayed study visits as a result of a delayed vaccination following a study pause are not considered to be protocol violations.

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 confirmed study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of IDMC members and coordination of an IDMC meeting in case of a study pause no later than 24 hours after becoming aware.

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 may initiate IDMC review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

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

Resumption of vaccinations will start only upon receipt of written recommendations by the IDMC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. These recommendations from the IDMC will be communicated to investigators, IRB/IEC and relevant health authorities, according to local standards and regulations.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants must not receive any further doses of study vaccine but should remain on study for follow-up of safety and immunogenicity as indicated in the Schedule of Activities (Section 1.3). 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 (other than scheduled unblinding) on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination

- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic (>14 days) or recurrent use of systemic corticosteroids and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal of consent/assent to receive further study vaccination (second vaccination of the 2-dose regimen)
- 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), GBS or MIS-C.
- Per the implementation of Amendment 1, the participant has a history of CLS.

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 or 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.

For those participants who are unable to continue participation in the study up to the last planned study visit, but for whom consent or assent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent or assent from participation in the study will be offered an optional visit for safety follow-up. This includes the safety assessments of the early exit visit (no blood sampling for immunogenicity).

Withdrawal of Consent or Assent

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

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information for each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members. A participant will be considered lost to follow-up if he or she repeatedly fail 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 or parent/caregiver to reschedule the missed visit as soon as possible, to counsel the participant or parent/caregiver 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 or parent/caregiver (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 (or their parent/caregiver) 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 or parent/caregiver to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

Adolescent participants will be provided access to an eCOA and given a SIC reference card to assist the participant. This eCOA will be used to collect COVID-19 signs and symptoms surveillance info, for PRO (SIC, including the highest body temperature recorded within 24 hours, blood oxygen saturation levels, and pulse rate) in case of COVID-19-like signs and symptoms, to collect data on 7-day reactogenicity (solicited signs and symptoms, including body temperature), and to collect suspected symptoms of TTS.

All PRO assessments (SIC, including body temperature and pulse oximetry results) should be conducted/completed before any tests, procedures, or other consultations to prevent influencing

participant responses. Refer to the Participant Instructions for instructions on the administration of PROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: first the SIC, then vital signs, then blood draws. Actual dates and times of assessments will be recorded in the source document and in the eCRF.

All participants will be provided with a thermometer (to measure body temperature) and 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. Adolescent participants will also be provided with a pulse oximeter to measure blood oxygen saturation and pulse rate during a COVID-19 episode. The reactogenicity 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 site staff is responsible for providing appropriate training to the participant on how to capture the data in the eCOA to avoid missing or incorrect data. The reactogenicity diary will be reviewed by the study personnel at visits indicated in Section 1.3. If the reactogenicity diary review is unavailable, the reactogenicity diary will be reviewed during the following visit. If a participant misses a vaccination, the reactogenicity diary covering the period after the missed vaccination does not have to be completed.

Blood draw volumes allow for an acceptable amount of blood to be collected in each participant throughout the study (EU 2008; EMA 2017; Howie 2011; Veal 2014; Peplow 2019; US FDA 2019). For adolescents with a positive molecular test result for SARS-CoV-2 infection (regardless of where the testing was performed), 2 additional serum samples for the assessment of humoral immunogenicity will be collected: 1 to 6 days after signs or symptom onset (COVID-19 Day 4 to 7) and on COVID-19 Day 29 (±7 days). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. In case there are difficulties collecting sufficient blood from adolescents, the following sequence should be followed: first serum, then PAXgene® tubes. For participants who experience a suspected AESI, up to an additional 30 mL of blood may be collected. Refer to the laboratory manual and Schedule of Activities (Section 1.3) for further details.

Study visits, other than screening and visits at which study vaccination is scheduled, may take place at the participant's home by site staff or a trained and delegated HCP if there are travel restrictions in case of an ongoing pandemic and if allowed by local regulations. The PI continues to be responsible for reviewing all protocol-related assessments. If home visits are not allowed by local regulations, procedures and activities may be done by other methods where possible (such as telephone or video conferencing).

Visit Windows

Visit windows are provided in Section 1.3. 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 6.8), efforts will be made to still vaccinate the participant, 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 would overlap with other scheduled visits, in which case the sponsor should be contacted and a case-by-case assessment is to be agreed upon.

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 both occur on Day 1. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination.

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study-specific screening consent process, but only if the relevant pre-screening tests are identical to the per protocol screening tests and are within 28 days prior to 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. Participants who test positive on the molecular test or the serological test (antibodies) will be informed of the result by the study site 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 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/IPPI

- Laboratory manual
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- eCOA platform access and user instructions (participants may use their own eDevice using an application if their device [smartphone or tablet] is compatible). Provisioned devices will be available on a limited basis
- Contact information pages

8.1. Immunogenicity Assessments

8.1.1. Immunogenicity Assessments

No generally accepted immunological correlate of protection has been demonstrated for SARS-CoV-2 to date. 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 be performed in addition, as outlined in a revised analytical plan. If the correlate or threshold of protection will be used as an endpoint the definition of seroconversion and seroconversion rate will be described in the SAP for the study.

Blood samples will be collected for assessment of humoral immune responses in all participants at the timepoints specified in the SoA. Blood sample timepoints and blood sample volumes are detailed in Section 8 and Section 1.3.

In case there are difficulties collecting sufficient blood, the following sequence should be followed: first serum, then PAXgene® tubes in case of a COVID-19 event.

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 for further details.

Immunogenicity assays may include, but are not limited to, the assays summarized in Table 3.

Table 3: Summary of Immunogenicity Assays (Part 1)

Assay	Purpose
Supportive of primary endpoints[a]	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to the SARS-CoV-2 S protein
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to wild-type virus and/or pseudovirion expressing S protein
Supportive of secondary/exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA) and/or equivalent assay	Analysis of antibodies binding to the SARS-CoV-2 S protein, or SARS-CoV-2 variant proteins
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to wild-type virus and/or pseudovirion expressing S protein, or SARS-CoV-2 variants
SARS-CoV-2 binding antibodies (ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to the SARS-CoV-2 N protein
Adenovirus neutralization (neutralization assay)	Analysis of neutralizing antibodies to adenovirus
Binding antibodies to S protein, N protein, RBD of S protein, of SARS-CoV-2 and other coronaviruses (MSD, ELISA or equivalent assay)	Analysis of antibodies to S, N, and the RBD of the SARS-CoV-2 S protein or SARS-CoV-2 variants, and coronaviruses other than SARS-CoV-2
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling	Analysis of cytokines, chemokines, and other proteins of the immune response in serum or plasma
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Gene expression analysis (RNA-seq)	Analysis of gene expression by RNA transcript profiling

ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig = immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; MSD = Meso Scale Diagnostics, LLC; RBD = receptor binding domain; VNA = virus neutralization assay

a. Either S-ELISA or VNA will be used to support the primary endpoint in Part 1.

A rapid SARS-CoV-2 serologic finger-prick test for past infection with SARS-CoV-2 will be performed for all participants at Day 1. Participants who test positive may be informed of the result by the study staff.[a] Participants who test positive will not be included.

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

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

Procedures to be performed in the event a participant experiences signs or symptoms suggesting possible COVID-19 (see Section 8.1.2.1), or a participant became aware of a positive RT-PCR test result for SARS-CoV-2 outside the study context, whether symptomatic or asymptomatic, are detailed in the Schedule of Activities in Section 1.3.3.

Note: if for any reason a site visit per the procedures described below is not feasible, a member of the study site staff can visit the participant at home (or at the hospital or other location, if needed), if allowed by local regulations. If site staff are unable to perform home visits, a trained and delegated HCP may perform the visits and assessments described below if allowed by local regulations. The PI continues to be responsible for reviewing all protocol-related assessments. Site staff/HCPs visiting participants at home will use personal protective equipment according to local regulations. If a home visit is not feasible, procedures and activities may be done by other methods where possible (such as telephone or video conferencing).

In case the participant experienced any signs or symptoms suggesting possible COVID-19, medical management of the case should follow local recommendations/guidelines.

The following procedures are specific for the study:

Day 1 to 3 Procedures in Case of Signs and Symptoms

If a participant records in the eCOA or informs the site that they experienced any signs or symptoms suggesting possible COVID-19, this will be considered **COVID-19 Day 1** (day of onset of signs and symptoms). The participant will be asked to complete the PRO (ie, the SIC, including body temperature and pulse oximetry) in the eCOA.

Notes:

For ease of completion, reference cards have been developed to describe some of the terms included in the SIC. (Refer to Section 10.7 for details)

The SIC questionnaire asks the participant if they had any of the prespecified signs or symptoms during the past 24 hours, and (when applicable) to rate the severity.

The participant should take the temperature of the participant in the evening at the same time each day and record their highest temperature in the last 24 hours in the SIC.

The participant should record at least 1 of the 3 pulse oximetry readings in the last 24 hours in the eCOA.

If a participant is unable to complete the SIC in the eCOA, a site staff member can collect information on the participant's signs or symptoms, body temperature, and pulse oximetry, over the telephone or visit of the participant at home (if allowed by local regulations), reading the questions aloud to the participant and entering the responses on the participant's behalf. More details are provided in the PRO completion guidelines.

Based on the information collected through the SIC, the site will reach out to the participant at the latest on COVID-19 Day 2 (the day after the day of signs/symptom onset) to assess whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria

(Section 8.1.2.1). As several of the prespecified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19. If the participant or parent(s)/caregiver(s) would actively reach out to the site already on COVID-19 Day 1, the site should already make a first assessment on COVID-19 Day 1 to check whether the reported signs and symptoms qualify as a suspected COVID-19 episode using prespecified criteria (Sections 8.1.2.1). As soon as the prespecified criteria for suspected COVID-19 are met (**COVID-19 Day 1 to 3**), the participant will be asked to undertake the COVID-19 procedures. In particular:

The participant will be asked to continue to complete the PROs in the eCOA, as specified above for COVID-19 Day 1:

- SIC (including body temperature): every day, preferably in the evening around the same time each day.
- Blood oxygen saturation and pulse rate using a pulse oximeter 3 times a day, preferably in the morning, at lunch time, and in the evening.

  Note: if the PROs are not able to be completed due to special circumstances, such as the adolescent being too ill, hospitalization or ventilation, the reason for not completing the PROs should be recorded by site staff in the eCRF.

A nasal swab and saliva sample (if feasible) will be collected from the participant by study site staff on **COVID-19 Day 1 to 3**, as soon as possible after it has been confirmed that the prespecified criteria for suspected COVID-19 are met. In case the nasal swab and saliva sample (if applicable) is taken at home, the study site should arrange transfer of the nasal swab and saliva sample (if applicable) to the study site as soon as possible after collection (within at most 24 hours).

Day 1 to 3 Procedures in Case of a Positive RT-PCR Test Outside the Study Site Context (Including a Positive RT-PCR Test of a Close Relative/Contact)

If a participant or a close relative/contact from the participant has a positive RT-PCR test for SARS-CoV-2 outside the study context, the participant or parent/caregiver should contact the site as soon as possible after becoming aware of the positive test. The day the participant or parent/caregiver became aware of the positive RT-PCR test will be considered **COVID-19 Day 1**. Regardless of whether the participant is symptomatic or asymptomatic, the participant will be asked to:

Complete the (suspected) COVID-19 surveillance (symptom check) in the eCOA. In case of COVID-19-like signs and symptoms they will need to complete the SIC including recoding body temperature and pulse oximetry in the eCOA.

In case of a positive RT-PCR test from a close relative/contact from outside the study: site staff will collect a nasal swab and saliva sample (if feasible) from the participant on **COVID-19 Day 1 to 3**, as described for participants with signs and symptoms (see above).

In case of a positive RT-PCR test for the participant from outside the study: the **COVID-19 Day 4 to 7** procedures will be initiated, as described below.

If a participant has a positive test result for SARS-CoV-2 infection, the participant will be notified. The participant may be requested to stay at home and not visit the study site. If necessary, study-site personnel will visit the participant at home[a] (if allowed by local regulations). The participant will be contacted by the site at least once per week to follow-up on the participant's condition and the participant's medical care provider will be notified. The SIC will be reviewed by site staff during these contacts (phone call or visit).

If a participant has a negative test result for SARS-CoV-2 infection, the participant will not undertake any further COVID-19 procedures and will fall back to the default Schedule of Activities (Section 1.3).

Day 4 to 7 Procedures for all Participants Who Have met the Prespecified Criteria for COVID-19 (see Section 8.1.2.1)

The participant will be asked to come to the site on **COVID-19 Day 4 to 7** (between 1 and 6 days after signs/symptom onset and becoming aware of a positive molecular test on COVID-19 Day 1 to 3) or a positive RT-PCR test from outside the study.

For all participants with confirmed COVID-19 (by molecular test), study staff will measure vital signs (body temperature, heart rate, and respiratory rate) and oxygen saturation (via pulse oximetry). A targeted physical examination will be performed based on the judgement of the investigator.

A nasal swab (only for participants who had a positive RT-PCR test from outside the study) and saliva sample (if feasible) will be collected from the participant by a trained member of the study site staff. In case the nasal swab and saliva sample (if applicable) is taken at home, the study site should arrange transfer of the nasal swab and saliva sample (if applicable) to the study site as soon as possible after collection (within at most 24 hours).

A blood sample for exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity and for exploration of antibody responses to infection with SARS-CoV-2 will be collected by study staff and the procedures for the 7-day cycles should be started (see below). The medical history and description of COVID-19 episode will be collected by interview with the participant.

Procedures During the 7-Day Cycles

If a participant has a positive nasal swab sample for SARS-CoV-2 at COVID-19 Day 1 to 3 or a positive RT-PCR test from outside the study, the participant will be asked to undertake the COVID-19 procedures, in particular:

In case of signs and symptoms: The participant will be reminded to further complete the PROs daily in the eCOA as described for COVID-19 Day 1 to 3.

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

In case of positive molecular test and asymptomatic: The participant will be reminded to further complete (suspected) COVID-19 surveillance (symptom check) at least twice a week.

A member of the study staff will collect a nasal swab and saliva sample (if feasible) from the participant once every 7 days*. If the sample is collected at home, the study site should arrange transfer of the nasal swabs and saliva sample (if applicable) to the study site as soon as possible after collections (within 3 days after collection)

Note: The participant should be encouraged by the site to allow the collection of nasal swabs and saliva sample (if feasible) from the participant as indicated in Section 1.3.3. If the participant is unable or unwilling to have all samples collected as requested, the participant should still complete the other COVID-19 assessments, including the visit at COVID-19 Day 29.

**Note*: Nasal swabs and saliva (if feasible) during the 7-day cycles may be collected at home by the participant (if sample pick up from the participant's home is feasible).

Day 29 Procedures

If a participant has a SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1 to 3 or from outside the study, then the participant will be asked to return to the site on COVID-19 Day 29 (±7 days) where a blood sample will be drawn from the participant for sero-confirmation, for exploration of antibody responses to infection with SARS-CoV-2, and exploration of biomarkers that correlate with SARS-CoV-2 infection and COVID-19 severity. Study staff will measure vital signs (body temperature, heart rate, and respiratory rate) and oxygen saturation (via pulse oximetry). A targeted physical examination will be performed based on the judgement of the investigator. The medical history and description of COVID-19 episode will be collected by interview with the participant. If the participant is still symptomatic, the participant will complete the SIC in the eCOA. For asymptomatic participants, the (suspected) COVID-19 surveillance (symptom check) will be completed by the participant.

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

Closure of the COVID-19 Episode

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

If the nasal swab collected from the participant on COVID-19 Day 1 to 3 is **negative** for SARS-CoV-2, the participant will not undertake any further COVID-19 procedures and will fall back to the default Schedule of Activities (Section 1.3).

If the participant has a SARS-CoV-2 positive nasal swab collected on COVID-19 Day 1 to 3 or from outside the study, then the participant will be asked to undertake the COVID-19 procedures until 14 days after signs or symptom onset/positive RT-PCT test from outside the study (COVID-19 Day 15, if applicable) or until **resolution of the**

COVID-19 episode, whichever comes last[a]. Resolution of the COVID-19 episode is defined as having 1 SARS-CoV-2 negative nasal swab and 2 consecutive days with no COVID-19-related signs or symptoms. Once past COVID-19 Day 15, nasal swabs and saliva sample will no longer be collected from the participant as soon as 1 nasal swab is SARS-CoV-2 negative, but (if the participant is still symptomatic at that time) the participant should continue completing the PROs (including SIC, body temperature, and pulse oximetry) in the eCOA until 2 consecutive days with no COVID-19-related signs or symptoms.

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

Upon closure of the COVID-19 episode and procedures, all participants will fall back to the default Schedule of Activities (Section 1.3). If the participant experiences new signs or symptoms suggesting possible COVID-19 at a later point in time, the participant would restart the COVID-19 procedures from COVID-19 Day 1 onwards (Section 1.3.3).

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

8.1.2.1. Prespecified Criteria for (Suspected) COVID-19 (Adolescents)

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

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

OR

A positive RT-PCR result for SARS-CoV-2 for a parent/caregiver, or any other close relative/contact of the participant, 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 by an alternative diagnosis and in the presence of a suspected exposure:

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

- Fever (≥38.0°C or ≥100.4°F) or chills
- Pulse oximetry value ≤95%, which is a decrease from baseline
- Tachycardia (according to age)
- Cough
- Nasal congestion or runny nose (rhinorrhea)
- Shortness of breath, difficulty breathing, or wheezing
- Diarrhea
- Vomiting
- Lethargy/tiredness/decreased activity
- Poor appetite or poor feeding
- Mood behaviors (frequently crying, irritability)
- Tachypnea (according to age)
- Bluish lips or face
- Red or bruised looking feet or toes
- New loss of taste or smell
- Muscle or body aches
- Neurologic symptoms (numbness, difficulty forming or understanding speech)
- Symptoms of blood clots: pain/cramping, swelling or redness in the legs/calves
- Other nonspecific symptoms such as: rash, bloodshot eyes or eye irritation/drainage, sore throat, stomachache, headache
- Clinical suspicion/judgement by investigator of symptoms suggestive of COVID-19, including MIS-C

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

8.1.3. Procedures for Adolescents Whose Close Relative/Contact Has Suspected or Confirmed COVID-19

Testing for SARS-CoV-2 should be performed for all adolescents, regardless of whether there are signs of infection in the adolescent if their parent/caregiver or close relative/contact from the same household has suspected or confirmed COVID-19, refer to the procedures in Section 8.1.2.

Testing of asymptomatic and symptomatic adolescents should be performed according to the procedures in Section 8.1.2, within 48 hours after becoming aware of a positive test from the parent/caregiver or the close relative/contact.

For adolescents presenting with signs of infection suggestive of COVID-19 (see Section 8.1.2.1), or with a positive SARS-CoV-2 test, refer to the procedures in Section 8.1.2.

8.1.4. Symptomatic SARS-COV-2 Infection

Identification and local molecular confirmation of SARS-CoV-2 infection and symptomatic COVID-19 will be performed throughout the study as described in Section 8.1.2 and 8.1.3. The PRO to evaluate exploratory vaccine efficacy parameters will be the SIC.

Molecular confirmation of SARS-CoV-2 infection will be performed for the exploratory analysis of the case definition. The severity of all COVID-19 cases will be assessed using the case definitions in Section 10.9.

8.1.5. Asymptomatic SARS-CoV-2 Infection

A non-S protein ELISA (eg, SARS-CoV-2 N-ELISA) or SARS-CoV-2 immunoglobulin assay will be performed to identify cases of asymptomatic SARS-CoV-2 infection (see also Table 3). This assay will be performed at the timepoints specified in the SoA (Section 1.3).

Any asymptomatic participant with a positive molecular test 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 molecular test result will need to be captured in the eCRF.

8.2. Safety Assessments

Details regarding the IDMC are provided in Section 10.3.6. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

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

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 qualified person. 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 (in accordance with the local standard of care for adolescents), pulse/heart rate, preferably supine systolic and diastolic blood pressure, respiratory rate, and blood oxygen saturation will be assessed.

Pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Pulse/heart rate measurements should be preceded by at least 5 minutes of rest (if feasible) in a quiet setting without distractions (eg, television, cell phones). Assessment of vital signs is recommended prior to blood sampling.

Participants will utilize a reactogenicity diary in the eCOA to record body temperature, preferably orally, measurements post-vaccination from the time of vaccination until 7 days after each vaccination.

Participants with (suspected) COVID-19 should measure blood oxygen saturation 3 times a day and body temperature daily (the highest temperature in the last 24 hours each day) and record it in the eCOA for the duration of follow-up of COVID-19 episodes (as defined in Section 8.1.2).

8.2.3. Pregnancy Testing

A urine pregnancy test for participants 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 a 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

8.2.4.1. Thrombosis With Thrombocytopenia Syndrome

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 10.12) 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 1.3.4.1 and Section 10.2). 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.

8.2.4.2. Multisystem Inflammatory Syndrome in Children

In case of MIS-C, 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 MIS-C AESI form (see Section 10.13) electronically per instructions in the eCRF completion guidelines. In addition, every effort should be made to collect and other applicable testing (central laboratory) (see the Schedule of Activities in Section 1.3.4.2 and Section 10.2). The investigator will review the laboratory test results to assist the investigation of the AESI.

See Section 8.3.6.2 for details on laboratory test details to be reported for an AE of MIS-C.

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

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, MAAEs, AESIs, and PQC can be found in Section 10.4.

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

All Adverse Events

All 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 reactogenicity diary as part of the eCOA, 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.

MAAEs are defined as AEs with medically-attended visits including hospital, emergency department, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic diseases will be collected as part of the MAAEs. MAAEs are to be reported for all participants from the first vaccination until 6 months after each vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.

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 as described in Section 6.8.

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 1 onwards, TTS (Section 8.3.6.1) and MIS-C (Section 8.3.6.2) are considered to be AESIs. Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/µL] [BC 2021], and MIS-C) 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 cases of TTS (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.

Serious adverse events, including those spontaneously reported to the investigator, must be reported using an SAE form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician

from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of 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.

Signs and symptoms of MIS-C will be monitored and reported as SAE in adolescents with (suspected) COVID-19 as confirmed by a positive molecular test result for SARS-CoV-2, and in adolescents whose parents/caregivers or close relatives/contacts have a prior (within 4-weeks) or current suspected or confirmed COVID-19. Further details on case definition and reporting of MIS-C in adolescents can be found in Section 10.8.

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

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

Study-site personnel, as well as parents and caregivers, should be instructed how to interpret signs and symptoms (eg, crying and pain) in their individual child. They will be instructed to report both specific and nonspecific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc). These nonspecific symptoms may be the only manifestations of some adverse reaction observed in adolescents. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (eg, nausea, pain, mood alterations) in younger or mentally-disabled adolescents could potentially be at risk for under- or mis-reporting.]

These events may or may not have been noted in the participant's reactogenicity diary.

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 reactogenicity diary.

After each vaccination, adolescents will remain under observation at the study site for at least 30 minutes (or longer if required by institutional/local practice) for the presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in a reactogenicity diary for 7 days post-vaccination. All participants will be provided with a reactogenicity diary and instructions on how to complete the reactogenicity diary (see Overview in Section 8). Reactogenicity diary information will be transferred to the sponsor. After review and verbal discussion of the initial reactogenicity 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 reactogenicity 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 reactogenicity diary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in the references (ECDC 2020; Ad26.COV2.S IB).

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 reactogenicity 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 or ≥100.4° F, as recorded in at least 1 measurement (Marcy 2004).

Participants will also be instructed on how to note signs and symptoms in the reactogenicity diary on a daily basis for 7 days post-vaccination (day of vaccination and the subsequent 7 days), for the following systemic 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 reactogenicity diary.

Medically-attended Adverse Events

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

For details about AESIs, refer to Section 8.3.6.

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

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

Adverse events, 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 AESIs 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 10.12. A suspected TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.14 OR,
- Thrombocytopenia, defined as platelet count below 150,000/µL (BC 2021)

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 1.3.4.1). 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 10.12 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 1.

8.3.6.2. Multisystem Inflammatory Syndrome in Children

The Multisystem Inflammatory Syndrome in Children (MIS-C) is considered to be an AESI.

Unlike adults, the vast majority of children with COVID-19 have mild symptoms. However, some children have a significant respiratory disease, and some children may develop a hyperinflammatory response similar to what has been observed in adults with COVID-19.

The CDC issued a Health Advisory on May 2020, that outlines the following case definition for MIS-C (CDC, 2020):

- An individual aged <21 years presenting with fever[a], laboratory evidence of inflammation[b], 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
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

In the event of a suspected (MIS-C) event, laboratory assessments (AAP 2020; CDC 2020l; Henderson 2020) are required to facilitate diagnosis and determine treatment options, including but not limited to:

- Levels of inflammatory markers in the blood, including elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) and ferritin, lactate dehydrogenase (LDH), and absolute lymphocyte count.
- Complete blood count and platelet count.
- B-type natriuretic peptide (BNP) or NT-proBNP (pro-BNP) and sodium,
- D-dimer

SARS-CoV-2 related syndromes in the pediatric population continues to evolve and recommendations provided in this document do not replace the importance of clinical judgment tailored to the unique circumstances of an individual patient.

8.4. Virology Assessments

The presence of SARS-CoV-2 infection in nasal swabs will be assessed by the local laboratory for case management. Molecular confirmation of SARS-CoV-2 infection (via molecular diagnostic RT-PCR or equivalent, referred to as 'molecular test' throughout the document) by a central laboratory will be used for the exploratory analysis of the case definition. Nasal swabs will also be used to determine the presence of SARS-CoV-2 viral variants using whole genome sequencing. In addition, saliva samples collected from participants during a confirmed COVID-19 episode may be tested for the presence of and quantification of SARS-CoV-2 by a central laboratory.

Nasal swabs collected from participants with COVID-19-like signs or symptoms will also be tested at the central laboratory to determine the presence of other respiratory pathogens using a broad respiratory pathogens panel. The results from this test may be shared with the study site.

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

[b] 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.

8.5. Biomarkers

Blood will be drawn at selected timepoints during the study for evaluation of biomarkers (eg, related to vaccine immunogenicity and SARS-CoV-2 infection including relations with COVID-19 disease severity, PAXgene®), as indicated in Section 1.3.

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 immunogenicity and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

No formal hypothesis testing is planned in Part 1. Descriptive statistics will be used to compare vaccine immunogenicity in adolescents from study VAC31518COV3006 versus vaccine immunogenicity in young adults (18 to 25 years of age) from study VAC31518COV3001 or VAC31518COV3009 and between study groups in VAC31518COV3006. Descriptive statistics will be used to summarize the safety and reactogenicity endpoints.

9.2. Sample Size Determination

With a sample size of 50 participants per group, the width of the 90% CI for the observed proportion of adverse events will vary between 5.8% and 24.8% depending on the observed proportion. Assuming pooling of adverse event data after the first dose of the 1- and 2-dose regimen, the width of this confidence interval will vary between 3% and 17.3% depending on the observed proportion (Table 4).

Non-binding guidelines on dose and regimen selection will be described in the SAP. Decision making on the optimal regimen will take safety and reactogenicity data, as well as any available immunogenicity data, and data from other Janssen clinical trials of Ad26.COV2.S into account.

Table 4 : 90% Two-sided CI for Possible Observed Rate of Adverse Events

Observed Rate	0%	5%	10%	25%	50%
50 Participants	(0, 5.8%)	(1.2%, 13.4%)	(4%, 19.9%)	(15.3%, 37%)	(37.6%, 62.4%)
100 Participants	(0, 3%)	(2%, 10.2%)	(5.5%, 16.4%)	(18%, 33.1%)	(41.4%, 58.6%)

9.2.1. Immunogenicity

The VNA and S-ELISA have been selected as primary endpoints and samples from participants (young adults and adolescents) will be analyzed using these assays. Correlation between S-ELISA and VNA and between other relevant humoral immunogenicity readouts will be evaluated. See Section 9.4.2 for immunogenicity endpoints.

9.2.2. Safety

While mild to moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further vaccine 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 5 for the considered number of participants.

Table 5 : Upper Limit of the 95% One-sided CI if no Cases are Observed for Different Sample Sizes

Sample Size	N=25	N=50	N=100	N=250	N=1,000
Upper Limit 95% one-sided CI	11.3%	5.8%	3.0%	1.2%	0.3%

CI = confidence interval, N = number of participants

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

The Full Analysis Set (FAS) will include all participants with at least one vaccine administration documented.

The Per Protocol Immunogenicity (PPI[a]) 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 samples obtained from participants after SARS-CoV-2 infection (if confirmed by molecular testing or non-S-ELISA [or equivalent assay]) occurring during the study after randomization (if applicable), after other SARS-CoV-2 vaccination outside the study, and samples obtained outside predefined windows will be excluded from the analysis set. Participants who were seronegative by local serology finger-prick test on Day 1 prior to study entry but were determined to be seropositive at baseline by central N- or S- serology testing will also be included in the PPI. More details will be provided in the SAP.

9.4. Statistical Analyses

The SAP will be finalized prior to the first database lock 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. Planned analyses are defined in Section 9.5.

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

For safety and immunogenicity analyses, results will be analyzed by vaccine group and will be performed by age group in adolescents. Immunogenicity subgroup analyses will also be performed by BMI, ethnicity, and other factors as will be described in the SAP.

9.4.2. Primary/Secondary Endpoints

Safety Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group and by age group (12 to 15, and 16 to 17). 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 study vaccine due to an AE, or who experience a severe AE, AESI, or an SAE (including MIS-C).

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

Vital Signs

Vital signs including temperature, pulse/heart rate, preferably supine systolic and diastolic blood pressure, and respiratory rate 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.

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 GMC [ELISA] or GMT [VNA]). 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. More details will be provided in the SAP.

S-ELISA or VNA may be used as endpoint for decision making on dose and regimen selection. Correlation between S-ELISA and VNA and between other relevant humoral immunogenicity readouts will be evaluated.

The immunogenicity analyses will be performed on the PPI population.

COVID-19 Infections and Severity

Symptomatic and asymptomatic infections will be descriptively presented.

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.

9.4.3. 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 Analyses

Part 1:

A first IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 1. A second IDMC analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 2.

Selected sponsor members will review group unblinded summaries of those data, as well as any available immunogenicity data up to 28 days post-dose 1 and 14 days post-dose 2.

A primary analysis of safety, reactogenicity and immunogenicity data up to 28 days post-dose 2 will be performed and the selected dose level will be determined for any future pediatric studies. The sponsor will be unblinded at the time of the primary analysis, but the blind will be maintained

at a participant and study site level up to the unblinding visit. Interim analyses may be performed for safety and/or immunogenicity, to facilitate decision making with regards to planning of future studies or for regulatory submission purposes.

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

The SAP will describe the planned analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

Ad26	adenovirus type 26
AdVAC®	adenoviral vaccine (vector platform)
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
ChIP	Chromatin immunoprecipitation
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
eCRF	electronic case report form(s)
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERD	enhanced respiratory disease
FAS	full analysis set
Fc	crystallizable fragment
FDA	Food and Drug Administration
FI	formalin-inactivated
FOIA	Freedom of Information Act
FWER	family-wise error rate
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMC	geometric mean concentration
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	health care practitioner
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
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS (-CoV)	Middle East respiratory syndrome (coronavirus)
MHRA	Medicines and Healthcare products Regulatory Agency
MIS-C	multisystem inflammatory syndrome in children
MSD	Meso Scale Diagnostics, LLC

N	nucleocapsid
NHP	nonhuman primate
PI	principal investigator
PPI	per protocol immunogenicity
PQC	product quality complaint
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
(q)RT-PCR	(quantitative) 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)
SDL	selected dose level
SIC	Symptoms of Infection with Coronavirus-19
SIPPM	site investigational product and procedures manual
SoA	Schedule of Activities
SRP/SRS	study responsible physician/scientist
SSG	Statistical Support Group
SUSAR	suspected unexpected serious adverse reaction
Th	T helper
TNF-α	tumor necrosis factor alpha
TTS	thrombosis with thrombocytopenia syndrome
US	United States
VAERD	vaccine associated enhanced respiratory disease
VNA	virus neutralization assay
vp	virus particle
WHO	World Health Organization

Definitions of Terms

COVID-19	COVID-19 is the disease caused by the virus SARS-CoV-2. COVID-19 refers to SARS-CoV-2 infection with symptoms, and can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multiorgan failure, and death. (US FDA 2020a,b).
eCOA	Electronic clinical outcome assessment. An umbrella term encompassing different types of outcomes assessments which may include the COVID-19 signs and symptoms surveillance question and Symptoms of Infection with COVID-19 Questionnaire (SIC) (as a PRO) in participants 12 to 17 years of age, and the reactogenicity diary (to record vaccine reactogenicity) in adolescents. The term eCOA is also used throughout the document to refer to the digital tool in which the clinical outcome assessments are collected (eg, via an app).
Observer-blind	The vaccine recipient and those responsible for analyzing the data are blinded.
PRO	Patient-reported Outcomes. Used to collect the patient-reported outcome data. This includes the SIC questionnaire (Symptoms of Infection with Coronavirus-19) and the recording of pulse oximetry results.
reactogenicity diary	Used to record solicited signs and symptoms by the participants.
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a case report form (CRF) as determined by the protocol. Data in this system may be considered source documentation.
Study Name Convention	In this document, studies are mostly referred to using the short study name (preceding letters and final digits of the study identifier) only (eg, COV2001).

10.2. Appendix 2: AESI Clinical Laboratory Tests

Samples will be taken according to the SoA in Section 1.3. The following tests may be performed:

Protocol-Required AESI Laboratory Assessments

Laboratory Assessments	Parameters for Participants Evaluated at Prespecified Study Timepoints and, in Addition, upon Experiencing a Suspected AESI
Performed locally (or centrally if local laboratory is not available) Blood sample obtained and tested at study Day 1, Day 29, Day 57, Day 71 (for all participants), for visits Day 184 and Day 198 (for Groups 1-3), AND Day 1/29 for each occurrence of any suspected AESI (TTS and/or MIS-C)	
Hematology	Whole blood sample for platelet count which at some sites may be part of a complete blood count with differential.
Suspected TTS AESI **Stored and performed centrally** Only analyzed if participant experienced suspected TTS, upon request from central study team: Blood sample obtained at Day 1/29 for each occurrence of suspected TTS AESI and for visits Day 1, Day 29, Day 57, Day 71 (for all participants), for visits Day 184 and Day 198 (for Groups 1-3)*.	
Clinical Laboratory Assessments (Section 8.2.4.1)	Serum/plasma samples for coagulation-related assays such as but not limited to: • Activated partial thromboplastin time • Prothrombin time • International normalized ratio • Fibrinogen • Lupus anticoagulant • Beta-2 glycoprotein • Anti-cardiolipin • D-dimers • Anti-PF4 • Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay) • Platelet activation assay (if HIT/PF4 is positive) • Homocysteine • ADAMTS13 Activity and Inhibitor Profile

Laboratory Assessments	Parameters for Participants Evaluated at Prespecified Study Timepoints and, in Addition, upon Experiencing a Suspected AESI
Suspected MIC-S AESI **Stored and performed centrally:** Only analyzed if participant experienced suspected MIS-C, upon request from central study team: Blood sample obtained at Day 1/29 for each occurrence of suspected MIS-C AESI and for visits Day 1, Day 29, Day 57, Day 71 (for all participants), for visits Day 184 and Day 198 (for Groups 1-3)*.	
Clinical Laboratory Assessments (Section 8.2.4.2)	• Serum/plasma samples for coagulation-related assays such as, but not limited to, D-dimers • Levels of inflammatory markers in the blood, including elevated ESR/CRP and ferritin, LDH, and ALC • B-type natriuretic peptide (BNP) or NT-proBNP (pro-BNP) • Sodium

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

AESI = adverse event of special interest; MIS-C = Multisystem Inflammatory Syndrome in Children;
TTS = thrombosis with thrombocytopenia syndrome

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 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 vaccination
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

Country Selection

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

Other Ethical Considerations

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

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process and Assent Form

Legal guardian(s) (as defined in Section 2), per local requirements must give written consent and the adolescent (minor) must give assent according to local requirements after the nature of the study has been fully explained and before the adolescent can be enrolled in the study. Assent must be obtained from adolescents (minors) capable of understanding the nature of the study depending on the institutional policies; it should be written in language appropriate to the adolescent'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.

The ICF(s) and assent form must be signed before performance of any study-related activity. The ICF(s) and assent form that 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 ICF 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 (as appropriate for age and per local regulations) as well as the legally acceptable representatives of potential participants (if applicable), 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 or assent 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 (if applicable) are authorizing such access. It also denotes that the participant and legal guardian (if applicable) agree to allow the participant's 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 vaccination with Ad26-based vaccines including Ad26.COV2.S, to understand SARS-CoV-2 infection, to understand differential vaccine responders, to develop tests/assays related to Ad26.COV2.S and SARS-CoV-2 infection, and to perform other tests/assays related to other Ad26-based vaccines and infection with other viruses. The research may begin at any time during the study or the post-study storage period.

Stored samples and other health recordings 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).

10.3.6. Safety Monitoring Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. The IDMC 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 IDMC

will consist of at least 1 medical expert in the relevant therapeutic area of pediatrics and at least 1 external statistician independent of the sponsor and not involved in the final analysis of the study who will prepare the data and perform all IDMC safety analyses for review by the IDMC. Committee membership responsibilities, authorities, and procedures will be documented in its charter.

The IDMC will review data as indicated in Section 4.1. IDMC safety reviews will be based on descriptive safety tables and listings from all accumulated safety data at that point in time. After each review, the IDMC will make recommendations regarding the continuation of the study. When appropriate, the conclusions of the IDMC will be communicated to the investigators, the IRB/IEC, and the national regulatory authorities.

Molecularly confirmed COVID-19 cases will be reported to the IDMC on a regular basis.

The IDMC responsibilities, authorities, and procedures will be provided in its charter.

Ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study pausing situation as outlined in Section 6.8, or at request of the sponsor's medical monitor or designee. The PI and sponsor's study responsible physician will inform the IDMC of any AE of concern.

If any pausing rule is met (refer to Section 6.8) 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, 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 unblinded and provided with the statistical analysis based on unblinded data. As the IDMC, they are independent to the company. The SSG may include a clinician, a statistician, a statistical programmer, and a regulatory person.

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 per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

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

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

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

Registration of Clinical Studies and Disclosure of Results

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

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

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

The sponsor will review 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 the 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 an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent and 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; study vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccination 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, reactogenicity diary to record solicited AEs, daily signs and symptoms surveillance question, SIC) will be recorded and will be considered source data. The participant's reactogenicity diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

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

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

10.3.11. Monitoring

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

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

sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, 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 study vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

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

Any respiratory tract infection that is not due to SARS-CoV-2 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, any (S)AEs caused by molecularly confirmed SAR-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.

Serious Adverse Event

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

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

- Is Medically Important*

*Medical and scientific judgement should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 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 vaccination 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).

If a participant receives a positive SARS-CoV-2 result from a private/off-study test during the study, and the positive result occurs within 28 days after vaccination, the event will be reported as an AE. If it occurs after 28 days, the event will be recorded as an SAE only if the event qualifies as serious. The participant can continue in the study if they choose to; however, this must be in accordance with local country and site level recommendations for COVID-19.

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

Adolescents (12 to 17 Years of Age)

All AEs and laboratory data will be coded for severity using a modified version of the Food and Drug Administration (FDA) grading table, based on the version of September 2007 (US DHHS FDA CBER 2007), included in Section 10.5, Toxicity Grading Scale.

For AEs not identified in the grading table, the following guidelines will be applied:

Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities and requires medical intervention
Grade 4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR ER visit or hospitalization

The severity of solicited signs and symptoms will be graded in the reactogenicity diary by the participant based on the severity assessment provided in the reactogenicity diary and then verified by the investigator using the toxicity grading scale in Section 10.5. (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 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: Toxicity Grading Scales in Adolescents (12 to 17 Years of Age)

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007) (US DHHS FDA CBER 2007).

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 judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting[#]	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization; Hypotensive shock
Nausea[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities	Hospitalization; Inability to perform basic self-care functions
Diarrhea[#]	2 – 3 loose stools or < 400 gms/24 hours	38– 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or oral rehydration necessary	Hospitalization; Hypotensive shock OR IV fluid replacement indicated
Headache[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Fatigue[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Myalgia[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions

[#] Revised by the sponsor.

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

10.6. Appendix 6: Contraceptive Guidance

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

Definition of Person of Childbearing Potential

A Person of Childbearing Potential

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

A Person Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is 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 person experiences menarche) or the risk of pregnancy changes (eg, a person of childbearing potential who is not heterosexually active becomes active), the participant should have a negative pregnancy test immediately prior to each study vaccine administration. Participants of childbearing potential must be practicing a highly effective method of contraception, as described throughout the inclusion criteria (Section 5.1).

For a participant who becomes pregnant, this information will be shared with the study participant's legal guardian if the participant's age is <18 years of age, as required by local regulations.

10.7. Appendix 7: Symptoms of Infection with Coronavirus-19

Symptoms of Infection with Coronavirus-19 (SIC) (adolescents 12 to 17 years of age)

To assist adolescents (12 to 17 years of age) with some of the symptom descriptions, a reference card is provided (COVID Survey Reference Card). A readability assessment determined the SIC is at a 6th grade reading level based on the Lexile Framework for Reading.

10.8. Appendix 8: 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 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 adolescent 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[a], laboratory evidence of inflammation[b], 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
- 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.

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

[b] 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

Common signs and symptoms associated with MIS-C include the following:

- Fever (fever ≥38.0°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 adolescents will have the same signs and symptoms, and some adolescents may have symptoms that are not listed here.

Immediate **emergency care** is required in the event of the adolescent 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)/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.

10.9. Appendix 9: Case Definitions for COVID-19

10.9.1. Case Definitions for Adolescents 12 to 17 Years of Age

10.9.1.1. 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 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
- Other nonspecific symptoms such as: rash, bloodshot eyes or eye irritation/drainage

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

Case Definition for Severe/Critical COVID-19

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

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

- 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 mm Hg)

  * 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 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Neurologic dysfunction includes: Gross impairment in motor, cognitive, or speech and language functions (LaRovere 2021). Other symptoms such as dizziness, somnolence, altered mental, status, lethargy.
- Hepatic and renal impairment includes: Lower levels of albumin and elevated levels of creatinine, alanine transaminase, and aspartate aminotransferase (Ahmed 2020)
- Admission to the ICU
- Death

10.9.1.2. Case Definition for Mild COVID-19

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

AND at any time during the course of observation:

- 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 10.9.1.1.

10.9.2. US FDA Harmonized Case Definition for COVID-19

If a participant presents with symptoms as those listed by the US FDA harmonized case definition (see Section 10.11, CDC 2020b), 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 (CDC 2020b) 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.

10.9.3. 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.

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

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.

Adolescents, regardless of age, with the following underlying medical conditions might also be at increased risk of severe illness compared with other children:

- Asthma or chronic lung disease
- Diabetes
- Genetic, neurologic, or metabolic conditions
- Sickle cell disease
- Congenital heart disease
- Immunosuppression (eg, primary immunodeficiency)
- Medical complexity (children with multiple chronic conditions that affect many organs of the body, or are dependent on technology and other significant supports for daily life)
- Obesity

This list is not exhaustive but intends to provide an overview of underlying medical conditions that might increase the risk for severe illness in adolescents.

[a] 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 28 February 2022.

10.11. Appendix 11: Symptoms of Coronavirus (US Centers for Disease Control and Prevention) in Children

The following extract shows symptoms of coronavirus infection in children as listed on the US CDC website dated 21 January 2021 and were still accurate at the time of finalization of this protocol:

(https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html)

The most common symptoms of COVID-19 in children are fever and cough.

The symptoms of COVID-19 are similar in adults and children and can look like symptoms of other common illnesses, like colds, strep throat, or allergies. The most common symptoms of COVID-19 in children are fever and cough, but children may have any of these signs or symptoms of COVID-19:

- Fever or chills
- Cough
- Nasal congestion or runny nose
- New loss of taste or smell
- Sore throat
- Shortness of breath or difficulty breathing
- Diarrhea
- Nausea or vomiting
- Stomachache
- Tiredness
- Headache
- Muscle or body aches
- Poor appetite or poor feeding, especially in babies under 1 year old

10.12. Appendix 12: 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)
☐ Hormone replacement therapy (including contraceptives)

[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

☐ Phlebitis
☐ Inflammatory bowel disease
☐ Diabetes mellitus
☐ Hypertension
☐ Lupus
☐ Myeloproliferative disorders
☐ Hyperlipidemia
☐ 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)
Complete blood count 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		
Anticardiolipin 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:

10.13. Appendix 13: MIS-C 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 MIS-C. Additional data may be requested by the sponsor for investigation of the event.

Adverse Event of Special Interest Questionnaire (AESIQ) for Multisystem Inflammatory Syndrome in Children

Date of Report: [dd-MMM-yyyy]

1. Adverse Event Description

Participant's clinical signs and symptoms

- ☐ Tachycardia
- ☐ Dyspnoea
- ☐ Tachypnoea
- ☐ Fever ≥ 38 C
- ☐ mucocutaneous findings (rash, red/cracked lips, and strawberry tongue)
- ☐ Cardiac conduction abnormalities
- ☐ Severe headache
- ☐ Altered mental status
- ☐ Edema of hands/feet
- ☐ Gastrointestinal symptoms
- ☐ Lymphadenopathy
- ☐ Conjunctivitis
- ☐ Cranial nerve palsies
- ☐ Paresthesias

☐ Other symptoms found during the physical examination:

Does the patient have an epidemiologic link to SARS-CoV-2 infection? ☐ No ☐ Yes, details:

2. Medical History and Concurrent Conditions

Provide details:

Does the participant have a diagnosis of rheumatic disease?	☐ No	☐ Yes, details:
Does the participant have a diagnosis of cancer?	☐ No	☐ Yes, details:
Has the participant been treated with immunomodulating therapy?	☐ No	☐ Yes, details:
Has the participant ever been admitted to an ICU?	☐ No	☐ Yes, details:
Does the participant have arrhythmia recorded in their medical record?	☐ No	☐ Yes, details:
Does the participant have a history of systemic juvenile idiopathic arthritis?	☐ No	☐ Yes, details:
Does the participant have a history of a previous clotting disorder or a diagnosis of a hypercoagulable state?	☐ No	☐ Yes, details:
Does the participant have a history of remote or recent thrombotic events?	☐ No	☐ Yes, details:
Does the participant have family or personal history of thrombophilia?	☐ No	☐ Yes, details:

Does the participant have any of the following genetic risk factors:

- ☐ Blood-clotting disorder
- ☐ Dysfibrinogenemia
- ☐ ABO blood types: A and B or Rh+
- ☐ Prothrombin gene mutation
- ☐ Anti-thrombin deficiency
- ☐ Thrombophilia
- ☐ Protein C or S deficiency
- ☐ Antiphospholipid syndrome
- ☐ Factor V Leiden mutation

Does the participant have any acquired risk factors:

☐ Altered mobility ☐ Morbid Obesity
☐ Recent trauma ☐ Recent surgery

If yes to any of the above, provide details:

3. Relevant results of diagnostic tests including laboratory tests, imaging, biopsies, etc. Provide details of the levels/conclusion, date performed, normal ranges, etc. 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)
C-reactive protein		
PT/INR/PTT		
Erythrocyte sedimentation rate		
Absolute lymphocyte count		
B-type natriuretic peptide		
Lactate dehydrogenase		
Complete blood count		
Platelet count		
Ferritin		
D-dimer		
Albumin level		
Troponin		
Procalcitonin		
Fibrinogen		
Von Willibrand factor antigen		
Electrocardiogram[a]		

a. For electrocardiogram, results at baseline should be provided if available.

Provide details of any additional diagnostic results:

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

At the time of protocol Amendment 1 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 (TOC).

Amendment 3 (28 February 2022):

Overall Rationale for the Amendment:
At the present time, the recommended schedule for individuals aged 18 years and above in the US for the EUA approved Ad26.COV2.S consists of a single dose primary vaccination, followed by a single booster dose as of two months or later. EMA also recently approved the administration of an Ad26.COV2.S booster dose, at least two months after the initial dose in people aged 18 years and above. The pandemic has shown that appearance of divergent variants may necessitate further boosting in addition to the current recommended primary schedules. Hence, the main purpose for this Protocol Amendment 3 is to investigate the safety and immunogenicity of a booster vaccination with Ad26.COV2.S, following a primary vaccination regimen in adolescents. Note that this amendment only pertains to changes to Part 1. Part 1 is ongoing and there is uncertainty on the immune responses elicited in adolescent participants who are given lower doses of Ad26.COV2.S; therefore, the sponsor wants to ensure participants in Part 1 receive a booster dose of Ad26.COV2.S at the predefined time. Part 2 of the protocol will be amended at a later date and will not commence until the amended version is approved by the respective Health Authorities.

Participants that received 1 active vaccination in the primary regimen will be given a booster vaccination as of 6 months after the last vaccination (vaccination 1) with active vaccine. The booster dose level for these participants will be 2.5×10^{10} vp per 0.5 mL.

Participants that received 2 active vaccinations in the primary regimen will be given a booster vaccination as of 12 months after the last vaccination (vaccination 2) with active vaccine. The booster dose level for these participants and the dose level and regimen for Part 2 will be based on the IDMC and sponsor review of safety and immunogenicity data generated post-dose 1 and post-dose 2. Booster vaccination may be performed earlier if some dose levels do not result in acceptable immunogenicity outcomes after second vaccination in which case the booster dose level will be 2.5×10^{10} vp per 0.5 mL. This is to ensure that the participants will receive their booster under prespecified protocol timelines irrespective of when the selection of the final dose level (for the booster at 12 months for participants that received 2 active vaccinations in the primary regimen and for Part 2) will occur. A dose level of 2.5×10^{10} vp per 0.5 mL is already being administered as a 2-dose regimen (56-day interval) as part of the primary vaccination regimen in this study. The evaluation of the primary vaccination regimen data by the IDMC and sponsor will further support the use of a single booster vaccination with the same dose.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5 and 6) Booster 12 Month Post-dose 2 4.1 Overall Design 4.2.1 Study-Specific Ethical Design Considerations 4.4 End of Study Definition 5.1 Inclusion Criteria 6.8 Study Vaccination Pausing Rules 9.2 Sample Size Determination 9.5 Planned Analyses	The option of receiving an additional vaccination after the primary regimen has been removed from Part 1. All participants in Part 1 will now be given a booster vaccination with Ad26.COV2.S as of 6 months (for participants who receive an active vaccination followed by placebo) or as of 12 months (for participants who receive 2 doses of active vaccination) after their last active vaccination depending on which group the participant was assigned.	See overall rationale for amendment.
1.3.1 Part 1: Dose Selection Cohort (Groups 1, 2 and 3) Booster 6 Months Post-dose 1 1.3.2 Part 1: Dose Selection Cohort (Groups 4, 5 and 6) Booster 12 Month Post-dose 2	Text has been added clarifying that if a participant becomes infected with SAR-CoV-2 during the study they can still receive a booster vaccination of Ad26.COV2.S according to local recommendations or 3 months after the participant has recovered.	Consistency across the COVID program.
2.3.1 Risks Related to Study Participation	Risk related to a 3rd Ad26.COV2.S vaccination has been added.	Alignment across studies.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Removed the seroresponse rate endpoint. Additional objectives have been added to Part 1/ 2 • Assessment of safety and reactogenicity post-booster • Humoral immune response (pre- and post-booster)	Serological response to vaccination includes the calculation of a seroresponse rate. As a result of introducing a booster vaccination to the study.
1.1 Synopsis 4.1 Overall Design	Footnote a has been updated in the vaccination schedule tables.	To align with the text in the synopsis and main body of the protocol.
1.1 Synopsis 8.1.1 Immunogenicity Assessments	The summary of Humoral Immunogenicity Assays has been updated (ie, moved binding Abs for other coronaviruses to binding Abs row and addition of ELISA or equivalent assay).	Clarifications were made to better reflect the assays that could be used.
1.1 Synopsis 9.5 Planned Analyses	Updated text around the planned analysis for Part 1. Text has been added to the definition of PPI that other SARS-CoV-2 vaccination outside the study and samples outside pre-defined windows are excluded from the analysis set.	Clarification
8.1.1 Immunogenicity Assessments	Text updated to reflect that PBMCs	Clarification

Section Number and Name	Description of Change	Brief Rationale
	will be collected in a subset of seronegative participants in Part 2.	
10.1 Appendix 1: Abbreviations and Definitions	Added the definition of observer-blind.	Clarification
10.3.6 Safety Monitoring Committees Structure	Removal of the last part of the paragraph on reporting of molecularly confirmed COVID-19 cases.	There is no arm monitoring possible without a placebo arm.
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 Adolescents	Minor corrections of the criteria have been made.	To align with the updated CDC recommendations.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Minor clarifications were also made throughout the protocol.	Minor errors were noted.

Amendment 2 (26 October 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is to remove the full placebo arms of the study due to the increasing availability of COVID-19 vaccines in adolescents globally. The Argentinian Health Authority (ANMAT) was the first Authority to provide feedback about the availability of the vaccines for adolescents in their Country; therefore, they have requested to put a hold on ongoing vaccinations at sites in Argentina and suggested to remove placebo arm of the study in that Country. As a result, participants who were enrolled in Argentina under Protocol Amendment 1 will be unblinded to whether they received active vaccine or placebo and given the option to stay in study or receive the COVID-19 vaccine via their national vaccination program. Since it is foreseeable that the same situation will occur in other Countries, the sponsor proactively decided to remove the placebo arm entirely from the study protocol. Under the new design, all participants will receive active treatments regardless of the allocation group. The changes implemented in this amendment may result in modifications of Part 2 in a future amendment. Additionally, changes have been made throughout the protocol per FDA feedback provided to the sponsor 17 September 2021.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.4 Part 2: 2-dose Regimen 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine for Participants in Placebo Group: Removed 7.2 Participant Discontinuation/Withdrawal From the Study 9.2 Sample Size Determination 9.2.1 Immunogenicity 10.3.6 Safety Monitoring Committees Structure	Removal of placebo group throughout the protocol.	Per Health Authority request and availability of vaccines for adolescents globally.
1.1 Synopsis 1.2 Schema 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.2 Sample Size Determination	Replaced placebo with a 2nd dose of $2.5x10^{10}$ to the group that was planned to receive $2.5x10^{10}$ (0.5mL) as a first vaccination and then placebo as a second vaccination.	To explore a 2 dose regimen to compare to the 2 dose regimen in study COV3009.
1.3.7.1 Participants With an AESI	Included thrombocytopenia as a suspected AESI.	Consistency across COVID-19 studies.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.1 Part 1: Dose Selection Cohort 1.3.3 Part 2: 1-dose Regimen 1.3.4 Part 2: 2-dose Regimen 1.3.5 After the Primary Vaccination Regimen 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.4 End of Study Definition 5.1 Inclusion Criteria 6.1 Study Vaccine(s) Administered	Changed cross-over vaccination to additional vaccination(s).	Cross-over vaccination was intended for the placebo groups which no longer applies with the removal of the placebo groups in Protocol Amendment 2.
1.1 Synopsis 1.2 Schema 1.3.1 Part 1: Dose Selection Cohort 1.3.4 Part 2: 2-dose Regimen 1.3.5 After the Primary Vaccination Regimen 4.1 Overall Design	Updated the 6 month and 12 month visits for the 2-dose regimens to occur 6 and 12 months after the second dose.	To align with other Phase 3 studies.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1 Immunogenicity Assessments	An exploratory endpoint to evaluate the immunogenicity against emerging variants has been added.	To assess the humoral immune response against emerging variants in adolescents.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	An exploratory endpoint to evaluate different definitions of seroresponse has been added.	Per FDA request.
2.3.1 Risks Related to Study Participation 7.1 Discontinuation of Study Vaccination 10.1 Appendix 1: Abbreviations and Definitions	Text has been added regarding the increased risk of Guillain-Barré Syndrome (GBS) following use of the Ad26.COV2.S vaccine.	Based on the emerging data following use of the Ad26.COV2.S vaccine, GBS has been identified as an adverse drug reaction for the use of Ad26.COV2.S vaccine.
4.2 Scientific Rationale for Study Design 6.2 Preparation/Handling/Storage/Accountability 6.3 Measures to Minimize Bias: Randomization and Blinding 6.4 Study Vaccination Compliance	Text was updated to show that the vaccine administrator is also unblinded.	Clarification
4.1 Overall Design 4.4 End of Study Definition	Study duration and completion definitions have been updated to reflect changes in the timings of visits.	Clarification
5.2 Exclusion Criteria	A history of Heparin-induced thrombocytopenia has been added as an exclusion criterion.	Per FDA request.
5.4 Screen Failures	Text has been added stating that participants who were enrolled into the placebo arm under Protocol Amendment 1 are given the option to rescreen into one of the active arms under Amendment 2.	Removal of the Placebo arm in the study under Protocol Amendment 2.
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding	Text added to note that the sponsor will be unblinded during the interim analysis.	Clarification

Section Number and Name	Description of Change	Brief Rationale
9.5 Planned Analyses		
6.8 Study Vaccination Pausing Rules	An additional pausing rule for suspected TTS, possibly related to the vaccine, has been added.	Per FDA request.
1.1 Synopsis 9.5 Planned Analyses	Planned analyses in Part 1 have been updated.	To accurately reflect the data to be reviewed by the IDMC and selected sponsor members in the first and second analyses, and to add a separate interim analysis.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Minor clarifications were also made throughout the protocol.	Minor errors were noted.

Amendment 1 (13 July 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is to focus on the adolescent cohort due to the availability of new information from VAC31518COV2001. In addition, and in alignment with feedback from the FDA guidance, this study amendment will allow non-inferiority comparison of adolescents from this study versus young adults (18 to 25 years of age) from efficacy trials. Therefore, adult participants and all participants <12 years of age have been removed. The dose schedule and dose levels have also been modified and all boosters removed. This study will now have 2 parts consisting of a Dose Selection Cohort and an Expansion Cohort in selected dose levels and dosing regimens.

This amendment also includes 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.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 Part 1: Dose Selection Cohort 1.3.2 Part 2: 1-dose Regimen (Active and Placebo Groups) 1.3.3 Part 2: 2-dose Regimen (Active and Placebo Groups) 2 INTRODUCTION 2.1 Study Rationale 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND	Removal of participants who are either adults or <12 years of age. Participants who are 12 to 17 years of age are identified as adolescents.	This study will use young adults from VAC31518COV3001 and VAC31518COV3009 as external controls and therefore will only enroll participants who are 12 to 17 years of age.

Section Number and Name	Description of Change	Brief Rationale
ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.2.1 Study-Specific Ethical Design Considerations 4.4 End of Study Definition 5 STUDY POPULATION 5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.3 Measures to Minimize Bias: Randomization and Blinding 6.5 Dose Modification 6.8 Prestudy and Concomitant Therapy 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.1 Immunogenicity Assessments 8.2.1 Physical Examinations 8.2.2 Vital Signs 8.3.2 Method of Detecting Adverse Events, Medically-attended Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events 8.5 Biomarkers 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.4.1 General Considerations 9.4.2 Primary/Secondary Endpoints 9.4.4 Other Analyses 9.5 Planned Analyses 10.3.3 Informed Consent Process and Assent Form 10.3.10 Source Documents 10.4.3 Severity Criteria 10.5 Appendix 5: Toxicity Grading Scales 10.6 6: Contraceptive Guidance 10.7 Appendix 7: Symptoms of Infection with Coronavirus-19 10.9 Appendix 9: Case Definitions for COVID-19 10.10 Appendix 10: Summary of Guidance from CDC Website on Underlying Medical Conditions That Lead or Might Lead to		

Section Number and Name	Description of Change	Brief Rationale
Increased Risk for Severe Illness From COVID-19		
1.1 Synopsis 1.3.1 Part 1: Dose Selection Cohort 1.3.2 Part 2: 1-dose Regimen (Active and Placebo Groups) 1.3.3 Part 2: 2-dose Regimen (Active and Placebo Groups) 2 INTRODUCTION 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.3 Justification for Dose 6.1 Study Vaccine(s) Administered 6.3 Measures to Minimize Bias: Randomization and Blinding 6.5 Dose Modification 6.9 Study Vaccination Pausing Rules 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.2.1 Immunogenicity 9.2.2 Safety 9.4.2 Primary/Secondary Endpoints 9.5 Planned Analyses	Change of the overall study design to introduce: • 2 parts (Dose Selection Cohort and an Expansion Cohort) with co-primary endpoints • Inclusion of a 1-dose regimen with 3 dose levels • Inclusion of 2 injection volumes for the 2.5×10^{10} vp dose level • Modification of the 2-dose regimen by introducing 3 dose-levels; removing sentinels; and removing booster vaccinations	The change in study design provides flexibility to the dosing regimens as well as allowing comparison with data from VAC31518COV3001 and VAC31518COV3009.
1.1 Synopsis 1.3.6.1 Participants With an AESI 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 6.8 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.4.1 Thrombosis With Thrombocytopenia Syndrome 8.3 Adverse Events, Serious Adverse Events, Medically-attended Adverse Events,	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 up to 3 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
Adverse Events of Special Interest, and Other Safety Reporting 8.3.1 Time Period and Frequency for Collecting Adverse Event, Medically-attended Adverse Event, Adverse Event of Special Interest, and Serious Adverse Event Information 8.3.2 Method of Detecting Adverse Events, Medically-attended Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events 8.3.3 Follow-up of Adverse Events, Medically-attended 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 (TTS) 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 10.12 Appendix 12: TTS AESI Form 10.14 Appendix 14: Thrombotic Events to be Reported as AESIs		
1.1 Synopsis 1.3.6.2 Multisystem Inflammatory Syndrome in Children (MIS-C) 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk	Multisystem Inflammatory Syndrome in Children (MIS-C) has been included as an AESI and a reason for pausing. Follow-up assessments will be performed in the event of a suspected AESI.	Some children with COVID-19 may develop a hyperinflammatory response leading to MIS-C. Therefore, additional reporting and data collection procedures are implemented to follow-up

Section Number and Name	Description of Change	Brief Rationale
Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 6.9 Study Vaccination Pausing Rules 7.1 Discontinuation of Study Vaccination 8.2.4.2 Multisystem Inflammatory Syndrome in Children 8.3.1 Time Period and Frequency for Collecting Adverse Event, Medically-attended Adverse Event, Adverse Event of Special Interest, and Serious Adverse Event Information 8.3.6.2 Multisystem Inflammatory Syndrome in Children 9.4.2 Primary/Secondary Endpoints 10.2 Appendix 2: Hematology Clinical Laboratory Tests 10.13 Appendix 13: MIS-C AESI Form		symptoms of MIS-C and identify cases of MIS-C.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1.1 Immunogenicity Assessments	Primary objectives and endpoints have been split for Part 1 and Part 2. Use of virus neutralization assay (VNA) titers has been added as an alternative to S-ELISA in the Part 1 and to replace S-ELISA in the Part 2 primary endpoints.	To improve clarity of endpoints. For Part 1, VNA is added to allow flexibility in the type of assay used for dose selection. For Part 2, VNA replaces S-ELISA to implement the use of a functional assay for NI assessment.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9 STATISTICAL CONSIDERATIONS	Addition of seroresponse rate as a second immunogenicity co-primary endpoint.	This addition has been made in response to FDA feedback.
1.1 Synopsis 1.3.5 Procedures for Participants With (Suspected) COVID-19 3 OBJECTIVES AND ENDPOINTS 8.4 Virology Assessments	Addition of sequencing of nasal swabs as an endpoint.	To assess SARS-CoV-2 sequence during a confirmed COVID-19 episode in adolescents.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Assessment of cellular and humoral immune response, and correlation between binding antibodies to SARS-CoV-2 have been moved from a secondary objective to an exploratory objective. Assessment of humoral immune response at all blood collection timepoints will	Assessment of cellular immune responses have been moved to exploratory endpoints as this assessment is no longer conditional for dose selection and recruitment of

Section Number and Name	Description of Change	Brief Rationale
	be performed in a subset of participants	the Expansion Cohort. Assessment of humoral immune responses at all time points in a subset of participants was added in response to FDA feedback to assess kinetics and persistence of humoral immune responses post vaccination.
1.1 Synopsis 8.1.1 Immunogenicity Assessments	Addition of "epigenetic sequencing" as a form of sequencing analysis.	To allow greater flexibility in the analysis methods.
1.1 Synopsis 9 STATISTICAL CONSIDERATIONS 9.1 Statistical Hypotheses	Updated the Decision Tree-based Hypothesis Testing figure.	Update due to the change in study design.
1.1 Synopsis 9 STATISTICAL CONSIDERATIONS	Sample size justification for Part 1 and Part 2	Update due to the change in study design.
1.1 Synopsis 8.1.1 Immunogenicity Assessments	Update to the Summary of Humoral Immunogenicity Assays	Clarification due to the change in study design.
1.3.5 Procedures for Participants With (Suspected) COVID-19	Clarification in the footnotes that central laboratory testing of nasal swabs for SARS-CoV-2 infection will be done only after a local positive test.	Clarification.
1.3.5 Procedures for Participants With (Suspected) COVID-19 8 STUDY ASSESSMENTS AND PROCEDURES	Additional information added to support procedures in case a participant cannot attend the study site due to COVID-19.	Clarification of procedures in case of travel restrictions due to the ongoing COVID-19 pandemic.
1.3.5 Procedures for Participants With (Suspected) COVID-19 8 STUDY ASSESSMENTS AND PROCEDURES	Clarification that adolescent self-sample collection is only 'if feasible' to indicate that if sites cannot support collection of the samples from the participants home, health care professional visits will be needed.	Alignment with other Phase 3 protocols.
2 INTRODUCTION 11 REFERENCES	Correction of reference citation and inclusion of 14 references in the list of references.	Correction.
1.3.1 Part 1: Dose Selection Cohort 1.3.2 Part 2: 1-dose Regimen (Active and Placebo Groups) 1.3.3 Part 2: 2-dose Regimen (Active and Placebo Groups) 4.2.1 Study-Specific Ethical Design Considerations 8 STUDY ASSESSMENTS AND PROCEDURES	The blood draw volumes have been updated for adolescents 12 to 17 years of age.	Update to the blood draw volumes based on regulatory guidelines applicable for pediatric participants 12 to 17 years of age.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Vaccination	Addition of an exclusion criterion and reason for discontinuation for capillary leak syndrome (CLS).	Based on emerging postmarketing safety data.
5.2 Exclusion Criteria	Addition of an exclusion criterion specific for Part 1 that excludes participants who are seropositive for SARS-CoV-2 antibodies	In Part 1 (Dose Selection Cohort), all participants must be seronegative at baseline for SARS-CoV-2 antibodies.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Addition of an exclusion criterion for participants with a history of blood dyscrasias, autoimmune disease, or on medication that can lead to dyscrasias or thrombotic events.	This addition has been made in response to FDA feedback.
5.2 Exclusion Criteria	Addition of an exclusion criterion for participants with a history of any serious, chronic, or progressive neurological disorders or seizures including Guillain-Barré syndrome.	This addition has been made in response to FDA feedback.
6.3 Measures to Minimize Bias: Randomization and Blinding	Removal of "site" as a stratification item.	Correction.
6.8 Prestudy and Concomitant Therapy	Wording is added to stipulate that the administration of any vaccines other than the study vaccine must be recorded.	Clarification.
10.1 Appendix 1: Abbreviations and Definitions	Reference to a paper format as an alternative of the eCOA has been removed.	A paper format of the eCOA is not available.
10.9.1.1 Case Definition for Moderate to Severe/Critical COVID-19	Update to case definitions for moderate and severe COVID-19.	Update based on emerging data.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-Aug-2022 13:50:47 (GMT)	Document Approval