Janssen Vaccines & Prevention B.V.*

Clinical Protocol

Protocol Title

A Randomized, Double-blind, Phase 3 Study to Evaluate 6 Dose Levels of Ad26.COV2.S Administered As a Two-Dose Schedule in Healthy Adults

Protocol VAC31518COV3003; Phase 3
AMENDMENT 7

VAC31518 (JNJ-78436735)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, B.V.; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Regulatory Agency Identifier Number(s):

IND: 22657
EudraCT NUMBER: 2020-005801-14

Status: Approved
Date: 16 September 2022
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-RIM-153625, 10.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	This document
Amendment 6	01 June 2022
Amendment 5	30 November 2021
Amendment 4	3 August 2021
Amendment 3	23 June 2021
Amendment 2	10 May 2021
Amendment 1	8 March 2021
Original Protocol	15 December 2020

Amendment 7 (This document)

Overall Rationale for the Amendment: The order of the sequential non-inferiority assessment hypothesis testing has been modified in this amendment. The main study recruited participants not previously infected by SARS-CoV-2 and not previously vaccinated with a COVID-19 vaccine to evaluate the non-inferiority of different dose levels on immune responses following 1 or 2 doses of Ad26.COV2.S. For the non-inferiority analysis set, participants were to remain N serology negative at the respective timepoint of the non-inferiority assessment. During the course of the study, an unexpectedly high number of participants had symptomatic or asymptomatic infections and would therefore be eliminated from the analysis affecting the power of the study to conclude non-inferiority. Participants that have been recruited in the sub study and were not previously infected with SARS-CoV-2 or vaccinated with a COVID-19 vaccine will be part of the non-inferiority analysis of the main study However, not all dose levels in the main study (6 dose levels) are represented in the sub study (4 dose levels). Consequently, dose level groups that are in common will have a larger sample size than those present only in the main study and will have a higher power to conclude non-inferiority. As the non-inferiority assessment follows a sequential hypothesis testing, the order of the sequential hypothesis testing has been modified in this amendment.

For all participants, given that approved COVID-19 vaccines exist for the adult population in all countries in which VAC31518COV3003 is being conducted, if participants need to receive 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. Once the primary analysis results are available (post vaccination 2), investigators will be notified to contact participants in groups who received a dose level of Ad26.COV2.S that did not meet non-inferiority post vaccination 2 to advise them that they should receive a booster of a COVID-19 vaccine that is licensed/authorized through their national COVID-19 vaccination health care program if not done already.

In addition, due to extensive follow up data available after vaccination across the Ad26.COV2.S program, including up to 12 months, the follow up in this protocol has been reduced from 12 months to 6 months after last vaccination.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.4.1 2-dose Vaccination Schedule for Participants in the Main Study 1.4.2 2-dose Vaccination Schedule for the Sub Study Participants 4.1 Overall Design 4.4 End of Study Definition 9.5 Planned Analyses	Reduction of the follow up period after last vaccination from 12 months to at least 6 months.	The Company has collected sufficient long-term follow-up safety information across the program.

Section number and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests		
1.1 Synopsis 4.1 Overall Design	Study duration has been changed from 13-15 months to at least 8 months and follow up changed from 12 to 6 months.	Due to the reduction of follow up from 12 to 6 months.
1.2 Schema for Participants in the Main Study 1.3 Schema for Participants in the Sub Study 1.4.1 2-dose Vaccination Schedule for Participants in the Main Study 1.4.2 2-dose Vaccination Schedule for the Sub Study Participants	Given the follow up period has been reduced to 6 months, there are some participants in the study who would have already had their 6-month visit. For those participants, a final phone call for safety follow up has been added.	To capture any additional safety information from participants who already had been in the study beyond 6 months post vaccination.
1.1 Synopsis 9.1 Statistical Hypotheses	Text has been added explaining the change in the sequential order of non-inferiority testing.	The $2.5x10^{10}$ vp dose will be tested before the $7x10^{10}$ vp in the sequential testing due to an increased risk to fail non-inferiority as a consequence of a smaller sample size in the $7x10^{10}$ vp group.
1.1 Synopsis 9.2 Sample Size Determination	Added the expected power based on % of dropout due to various reasons (eg, lost to follow-up, participants with major protocol deviations with impact on immunogenicity, participants who become N-seropositive during the study or with a confirmed SARS-CoV-2 infection, and participants who received their vaccination outside the allowed window). Also, an explanation for the possible addition of the sub study participants in the primary analysis has been added.	The power calculations show why the sub study participants need to be added to the main study primary analysis for non-inferiority.
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding9.5 Planned Analyses	Text has been added stating results from the main and sub study may be reported together rather than in separate reports.	Clarification that the results from the main and sub study may be available at the same time.
1.1 Synopsis 2.1 Study Rationale 3 OBJECTIVES AND ENDPOINTS 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.2.1 Immunogenicity 9.4.2 Primary Endpoint(s)	The order of the sequential hypothesis testing has been modified.	To reduce the increased risk to fail non-inferiority as a consequence of a smaller sample size in the $7x10^{10}$ vp group.
1.1 Synopsis 9.5 Planned Analyses	Made clear that the Sponsor would be unblinded to the data for the main and sub study at the primary analysis stage.	Clarification
1.1 Synopsis 6.6 Continued Access to Study Vaccine After the End of Study	Participants that do not meet non-inferiority in the group they have been assigned will no longer be offered a booster of study vaccine	Currently there are several authorized COVID-19 vaccines available. The participants are advised to receive a booster dose

Section number and Name	Description of Change	Brief Rationale
	but rather are being advised to receive a nationally authorized/licensed vaccine outside of the study. All other participants are recommended to receive a booster outside the study, if needed, after the primary analysis.	following their national vaccination scheme including follow up.
1.4.1 2-dose Vaccination Schedule for Participants in the Main Study 1.4.2 2-dose Vaccination Schedule for the Sub Study Participants 8 STUDY ASSESSMENTS AND PROCEDURES	Total blood volume has been adjusted.	Due to the shorter follow up period post vaccination.
1.4.1 2-dose Vaccination Schedule for Participants in the Main Study 1.4.2 2-dose Vaccination Schedule for the Sub Study Participants	Humoral serum samples can be used for N serology testing.	Clarification to add flexibility that humoral samples may be used for N serology testing.
9.3 Populations for Analysis Sets 9.4.2 Primary Endpoint(s)	The definition of the non-inferiority (NI) analysis set has been added.	To define the NI analysis set.
9.4 Statistical Analyses 9.4.2 Primary Endpoint(s)	There will only be one SAP describing the analyses for the main and sub study. Additional text has been added to explain further how the non-inferiority analysis will be conducted if a large number of participants are N-seropositive.	Clarification Clarification
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.1 Immunogenicity Assessments	Additional exploratory endpoint in the main and sub study added to allow for assessment of Spike circulating protein	To allow for the assessment of Spike circulating protein following vaccination
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and clarifications were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Phase 3 Study to Evaluate 6 Dose Levels of Ad26.COV2.S Administered As a Two-Dose Schedule in Healthy Adults

Ad26.COV2.S (also known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein, stabilized in its prefusion conformation, which will be assessed in this study.

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

OBJECTIVES AND ENDPOINTS FOR PARTICIPANTS IN THE MAIN STUDY

Objectives	Endpoints
Primary	
To demonstrate non-inferiority (NI) in the following sequential order: • NI after 1-dose of Ad26.COV2.S $9x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $2.5x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $7x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $3.5x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1-dose of Ad26.COV2.S $1.25x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)	• Binding antibody concentrations to SARS-CoV-2 S protein as measured by ELISA 28 days after vaccination • NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 28 days post-dose 1, using a NI margin of 2/3 for the GMC ratio (GMC $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, , or $1.25x10^{10}$ vp/GMC $5x10^{10}$ vp)
To demonstrate NI in the following sequential order: • NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp vs 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)	• Binding antibody concentrations to SARS-CoV-2 S protein as measured by ELISA 14 days after vaccination 2 • NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 14 days post-dose 2 ($9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, , or $1.25x10^{10}$ vp) and 28 days post-dose 1 or 14 days post-dose 2 ($5x10^{10}$ vp), using a NI margin of 2/3 for the GMC ratio (GMC $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp)/GMC $5x10^{10}$ vp)

Objectives	Endpoints
• NI after 2-doses of Ad26.COV2.S 2.5x10^{10} vp vs 2-doses of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 7x10^{10} vp vs 1 dose of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 7x10^{10} vp vs 2-doses of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 3.5x10^{10} vp vs 1 dose of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 3.5x10^{10} vp vs 2-doses of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 1.25x10^{10} vp vs 1-dose of Ad26.COV2.S 5x10^{10} vp (release titer) • NI after 2-doses of Ad26.COV2.S 1.25x1010 vp vs 2-doses of Ad26.COV2.S 5x1010 vp (release titer)	
Secondary	
To assess the humoral immune response and durability to Ad26.COV2.S across all groups, at all blood collection timepoints.	• Serological response to vaccination and binding antibody GMCs to SARS.COV-2 S protein as measured by ELISA, or equivalent assay
To assess the safety and reactogenicity of Ad26.COV2.S administered at several dose levels.	• Solicited local and systemic AEs for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • SAEs throughout the study (from first vaccination until end of the study) • Adverse events of special interest (AESIs [from first vaccination until end of the study]) • MAAEs (until 6 months post-dose 2) • AEs leading to study discontinuation (during the entire study) for all participants following vaccination
Exploratory	
To further explore humoral immune responses to Ad26.COV2.S across all groups at all or selected blood collection timepoints.	Exploratory analyses may include the following: • SARS-CoV-2 neutralization as assessed by SARS-CoV-2 neutralization assays VNA (wtVNA and/or psVNA) including

Objectives	Endpoints
	neutralization of emerging SARS-CoV-2 variants • SARS-CoV-2 binding antibodies against emerging SARS-CoV-2 variants as assessed by S-ELISA or equivalent assay • Adenovirus neutralization • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass and IgG isotype • Analysis of circulating Spike protein • 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
To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints
To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of participants with positive non-S protein ELISA or equivalent assay (eg, nucleocapsid [N] protein ELISA)
To examine the immune response in vaccinated individuals with prior or breakthrough infection.	• SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein
To assess hematology laboratory parameters before and after Ad26.COV2.S administration.	• Including but not limited to: Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers, and anti-PF4

GMC=geometric mean concentration

OBJECTIVES AND ENDPOINTS FOR PARTICIPANTS IN THE SUB STUDY

Objectives	Endpoints
Secondary	
To assess the humoral immune response and durability to Ad26.COV2.S across all groups in the sub study, at all blood collection timepoints.	• Serological response to vaccination and binding antibody GMCs to SARS.COV-2 S protein as measured by ELISA, or equivalent assay
To assess the safety and reactogenicity of Ad26.COV2.S administered at several dose levels.	• Solicited local and systemic AEs for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • SAEs throughout the study (from first vaccination until end of the study) • Adverse events of special interest (AESIs [from first vaccination until end of the study]) • MAAEs (until 6 months post-dose 2)
Exploratory	
To further explore humoral immune responses to Ad26.COV2.S across all groups in the sub study at all or selected blood collection timepoints.	Exploratory analyses may include the following: • SARS-CoV-2 neutralization as assessed by SARS-CoV-2 neutralization assays VNA (wtVNA and/or psVNA) including neutralization of emerging SARS-CoV-2 variants • SARS-CoV-2 binding antibodies against emerging SARS-CoV-2 variants as assessed by S-ELISA or equivalent assay • Adenovirus neutralization • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass and IgG isotype • Analysis of circulating Spike protein • 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
To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints

Objectives	Endpoints
To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of participants with positive non-S protein ELISA or equivalent assay (eg, nucleocapsid [N] protein ELISA)
To examine the immune response in vaccinated individuals with prior or breakthrough infection	• SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein
To evaluate the innate, pro-inflammatory and other potentially relevant responses to Ad26.COV2.S vaccination at selected timepoints.	• Analysis of messenger ribonucleic acid (mRNA) expression levels of vaccine-induced innate responses including inflammatory and coagulation-related mediators • Analysis of cytokines, chemokines, and other protein- or lipid mediators of the innate immune response
To assess hematology laboratory parameters before and after Ad26.COV2.S administration.	• Including but not limited to: Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers, and anti-PF4

Ad26=adenovirus 26; GMC=geometric mean concentration

If a correlate or threshold for protection against COVID-19 is established in terms of humoral immunity, then a statistical comparison to that correlate or threshold will substitute non-inferiority testing to immune responses to vaccine at release, as outlined in a revised analytical plan.

Hypotheses

Formal non-inferiority (NI) testing will be applied to demonstrate NI of 1-dose and 2-doses of 9×10^{10} vp, $2.5x10^{10}$ vp, 7×10^{10} vp, $3.5x10^{10}$ vp, and $1.25x10^{10}$ vp Ad26.COV2.S versus 1-dose and 2-doses of $5x10^{10}$ vp Ad26.COV2.S (release titer), using a NI margin of 2/3 for the GMC ratios.

OVERALL DESIGN

Main Study

This is a randomized, double-blind Phase 3 study to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults. In this main study, the safety, reactogenicity, and immunogenicity of 1 dose (dose 1 of the 2-dose regimen) and 2-doses of Ad26.COV2.S will be evaluated. The lower dose ($3.5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) levels mimic vaccine degradation to enable determination of product expiry. In order to increase the end of shelf-life specifications a potential target release titer of $7x10^{10}$ vp will be evaluated. A higher titer of $9x10^{10}$ vp will also be evaluated as is the upper limit of the release range (potential maximum vp at release). The study population will consist of healthy men and women aged between 18 and 55 years (inclusive), who have not previously received a vaccine against COVID-19 and have not had prior exposure to SARS-CoV-2 as assessed by local serology testing. Participants will receive Ad26.COV2.S administered IM.

A target of approximately, 1,350 participants (225 participants per active vaccine group) in the main study will be randomized in parallel in a 1:1:1:1:1:1 ratio to 1 of 6 vaccination groups in this study. Participants

will receive a 2-dose vaccination regimen at different dose levels (9×10^{10} vp, 7×10^{10} vp, 5×10^{10} vp, $3.5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp).

Table: Schematic Overview of Study Design and Groups for the Main Study

Group	N	Day 1 Vaccination 1	Day 57 Vaccination 2
1	For NI ~ 225	Ad26.COV2.S $9x10^{10}$ vp	Ad26.COV2.S $9x10^{10}$ vp
2	For NI ~ 225	Ad26.COV2.S $7x10^{10}$ vp	Ad26.COV2.S $7x10^{10}$ vp
3	For NI ~ 225	Ad26.COV2.S $5x10^{10}$ vp	Ad26.COV2.S $5x10^{10}$ vp
4	For NI ~ 225	Ad26.COV2.S $3.5x10^{10}$ vp	Ad26.COV2.S $3.5x10^{10}$ vp
5	For NI ~ 225	Ad26.COV2.S $2.5x10^{10}$ vp	Ad26.COV2.S $2.5x10^{10}$ vp
6	For NI ~ 225	Ad26.COV2.S $1.25x10^{10}$ vp	Ad26.COV2.S $1.25x10^{10}$ vp

Sub Study

An additional enrollment of adult participants 18 to 55 years, inclusive, will enroll into a sub study, into Groups 1, 3, 5 and 6 to further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events. Participants will receive Ad26.COV2.S administered IM.

A target of approximately 240 participants will be enrolled in the sub study and will receive a 2-dose vaccination regimen at either 9×10^{10} vp, 5×10^{10} vp, $2.5x10^{10}$ vp, or $1.25x10^{10}$ vp. This target may not be met due to the challenges of enrolling seronegative subjects into the study, so sub-study enrollment may stop at lower numbers.

Table: Schematic Overview of Study Design and Groups for the Sub Study

Group	N (Seronegative)*	N (Seropositive)	Day 1 Vaccination 1	Day 57 Vaccination 2
1	~ 40	~ 20	Ad26.COV2.S $9x10^{10}$ vp	Ad26.COV2.S $9x10^{10}$ vp
3	~ 40	~ 20	Ad26.COV2.S $5x10^{10}$ vp	Ad26.COV2.S $5x10^{10}$ vp
5	~ 40	~ 20	Ad26.COV2.S $2.5x10^{10}$ vp	Ad26.COV2.S $2.5x10^{10}$ vp
6	~ 40	~ 20	Ad26.COV2.S $1.25x10^{10}$ vp	Ad26.COV2.S $1.25x10^{10}$ vp

*Due to the challenges of enrolling seronegative subjects into the study, study enrollment may stop at lower numbers.

An IDMC has been commissioned for the Ad26.COV2.S program. Any significant safety information will be shared with the IDMC.

The study duration from screening until the last follow-up visit will be at least 8 months per participant. The study will consist of a 28-day screening phase with vaccinations on Day 1 and Day 57, and a follow-up through at least 6 months after the last vaccination.

End of Study Definition

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

NUMBER OF PARTICIPANTS

Overall, a target of approximately 1,350 adult participants aged 18 to 55 years, inclusive, will be enrolled in the main study. A total of a target of approximately 240 participants 18 to 55 years, inclusive, will be enrolled in the sub study.

DOSAGE AND ADMINISTRATION

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

- Ad26.COV2.S will be supplied at a concentration of $2x10^{11}$ vp/mL as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer of Ad26.COV2.S will be supplied as diluent. Dose levels throughout the different groups will be $9x10^{10}$ vp, $7x10^{10}$ vp, $5x10^{10}$ vp, $3.5x10^{10}$ vp, $2.5x10^{10}$ vp and $1.25x10^{10}$ vp.

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

IMMUNOGENICITY EVALUATIONS

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

Table: Summary of Humoral Immunogenicity Assays[a]

Assay	Purpose
Humoral Immunogenicity	
Primary/Secondary/Exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein)
Exploratory endpoints	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein, including emerging SARS-CoV-2 variants.
SARS-CoV-2 binding antibodies (ELISA or equivalent assay)	Analysis of binding antibodies to SARS-CoV-2 proteins (eg, S-protein), including emerging SARS-CoV-2 variant proteins.
SARS-CoV-2 binding antibodies (non-S ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to the SARS-CoV-2 N protein
Adenovirus neutralization	Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling, and analysis of circulating Spike protein	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma, and analysis of circulating Spike protein
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Innate Assessments (*Exploratory endpoints)*	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in whole blood (ex vivo, PaxGene tubes)
Proteomic and/or lipidomic approaches, and analysis of circulating Spike protein	Analysis of protein translates (including circulating Spike protein) or lipid mediators in serum or plasma.

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

[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 serological testing outside the study.

SAFETY EVALUATIONS

After each vaccination, participants will remain under observation at the study site for at least 15 minutes for the presence of any acute reactions and solicited events. Participants will be asked to note in the diary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 7 days post vaccination (day of vaccination and the subsequent 7 days). Participants will also be instructed on how to note signs and symptoms in the diary on a daily basis for 7 days post vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, and myalgia.

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

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. Thrombosis with thrombocytopenia syndrome is considered to be an AESI. Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/μL[a]]) will be reported from the moment of vaccination until the end of the study/early withdrawal. An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS. All other unsolicited AEs will be reported for each vaccination from the time of vaccination until 28 days post vaccination. All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) will be reported from the moment of first vaccination until completion of the participant's last study-related procedure.

MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic diseases will be collected as part of the MAAEs. MAAEs are to be reported from the moment of vaccination until 6 months after the vaccination.

STATISTICAL METHODS

The number of participants chosen is to provide sufficient power for the non-inferiority comparisons.

The following assumptions were made in the sample size determinations:

- Log transformed (log10 scale) immune response data are normally distributed
- A common standard deviation (SD): SD=0.5 (log10 scale) of the immune response log transformed data
- Non-inferiority margin = log10(2/3) = -0.176
- Alpha = 0.0125 (1-sided) for 1- and 2-dose NI comparisons
- Power = 90%

Based on the above assumptions, a sample size of 225 per group is needed (assuming a 10.2% dropout rate) to detect non-inferiority with 90% power. An additional 40 seronegative and 20 seropositive participants per Groups 1, 3, 5, and 6 (a target of approximately 240 participants) will be enrolled to further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events.

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

The primary objective of this study is to demonstrate the NI, in terms of humoral immune response, of 1-dose and 2-doses of $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, and $1.25x10^{10}$ vp Ad26.COV2.S versus 1-dose and 2-doses of $5x10^{10}$ vp Ad26.COV2.S (release titer).

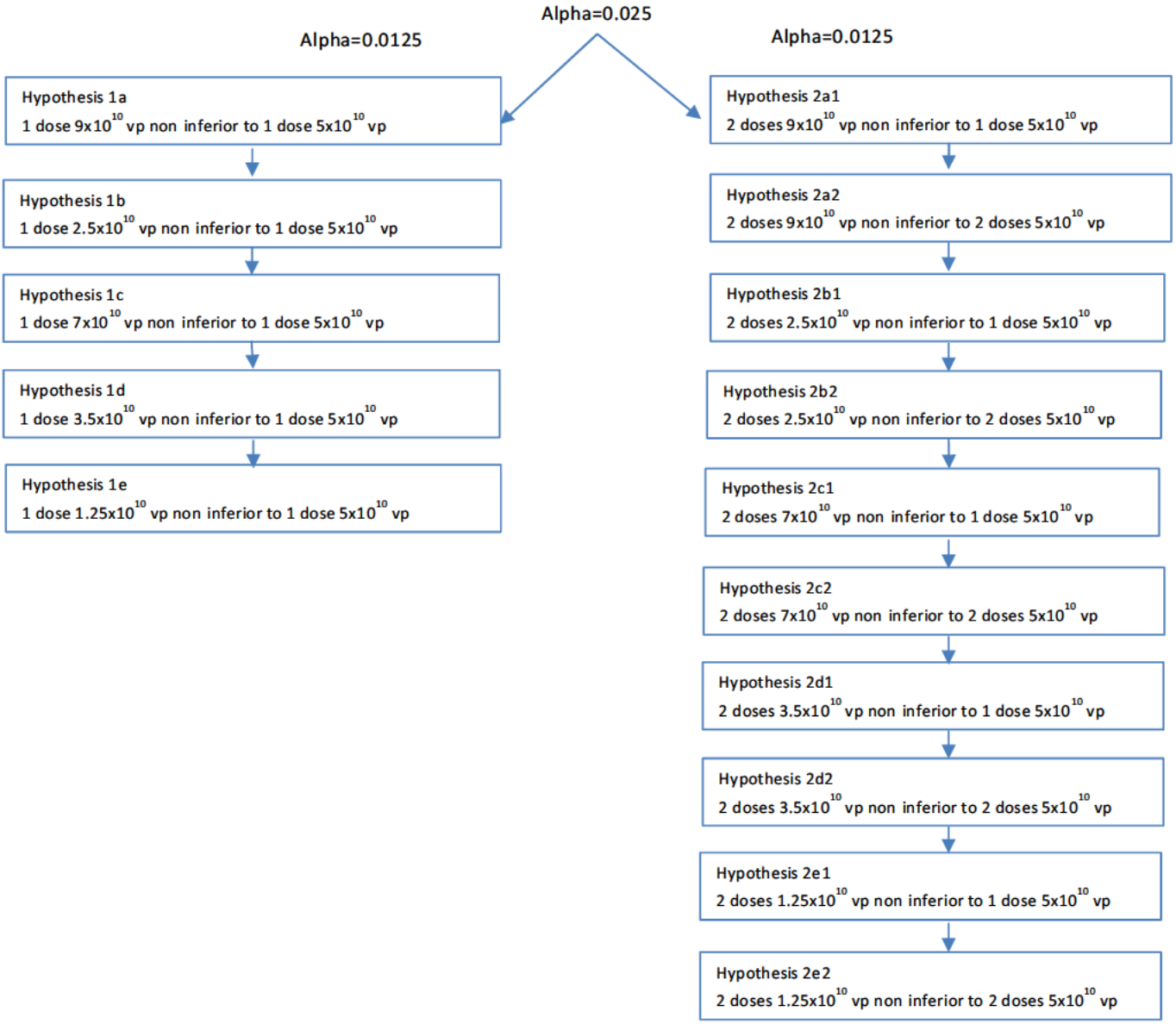
Participants in the main study and sub-study (participants who are seronegative at enrollment or baseline) may be combined for the analysis.

The table below shows how the power will be affected with 10%, 20%, 30%, 40%, 50% and 60% dropout due to various reasons (eg, lost to follow-up, participants with major protocol deviations with impact on immunogenicity, participants who become N-seropositive during the study or with a confirmed SARS-CoV-2 infection, and participants who received their vaccination outside the allowed window).

Table: Power Based on % of Drop Out

			% drop out since enrollment					
Regimen	**sample size at enrollment per arm**	**group**	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**
$9x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	1	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$2.5x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	5	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$7x10^{10}$ vp (main study)	212	2	89.40%	85%	79.90%	72.70%	63.70%	53.00%
$5x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	3	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$3.5x10^{10}$ vp (main study)	212	4	89.40%	85.00%	79.90%	72.70%	63.70%	53.00%
$1.25x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	6	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%

Figure: Decision Tree-Based Hypothesis Testing



Planned Analyses

The sponsor may be unblinded for this study, but the blind will be maintained at the participant and study site level up to study end.

The primary analysis, which will be performed on unblinded data, will include safety up to Day 85 and immunogenicity up to Day 71 in the main study and sub study for all groups and will be performed when all participants have completed the visit that takes place 85 days after the first study vaccination or discontinued earlier.

The final analysis for the main study will be performed when all included participants from the main study have completed their last visit (at least 6 months post last vaccination) or discontinued earlier. Results from participants in the sub study may be available with the main study. Results from the main study and sub study may be combined in one report.

Depending on availability of results, primary and final analysis might be combined.

Further 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.

For all participants, given that approved COVID-19 vaccines exist for the adult population in all countries in which VAC31518COV3003 is being conducted, if participants need to receive 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. Once primary analysis results are available (post vaccination 2), investigators will be notified to contact participants in groups who received a dose level of Ad26.COV2.S that did not meet non-inferiority post vaccination 2 to advise them that they should receive a booster of a COVID-19 vaccine that is licensed/authorized through their national COVID-19 vaccination health care program if not already received.

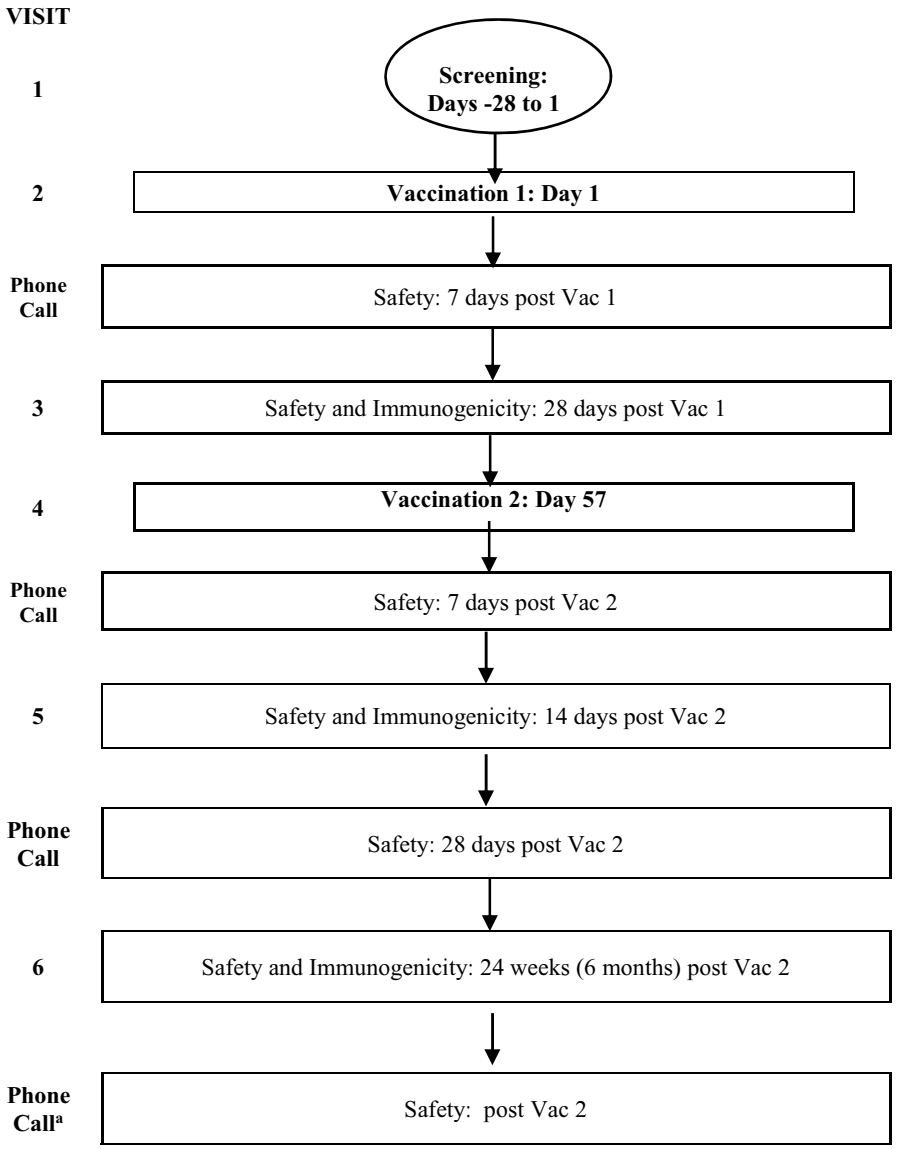
Unblinding due to availability of an authorized/licensed COVID-19 vaccine

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

If the participant prefers another company's vaccine, they will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event of the participant unblinding in order to receive an authorized/licensed COVID-19 vaccine, no further study vaccination will be permitted. Unblinded participants will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit. Safety 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 and immunogenicity analysis, as described in the Statistical Analysis Plan (SAP).

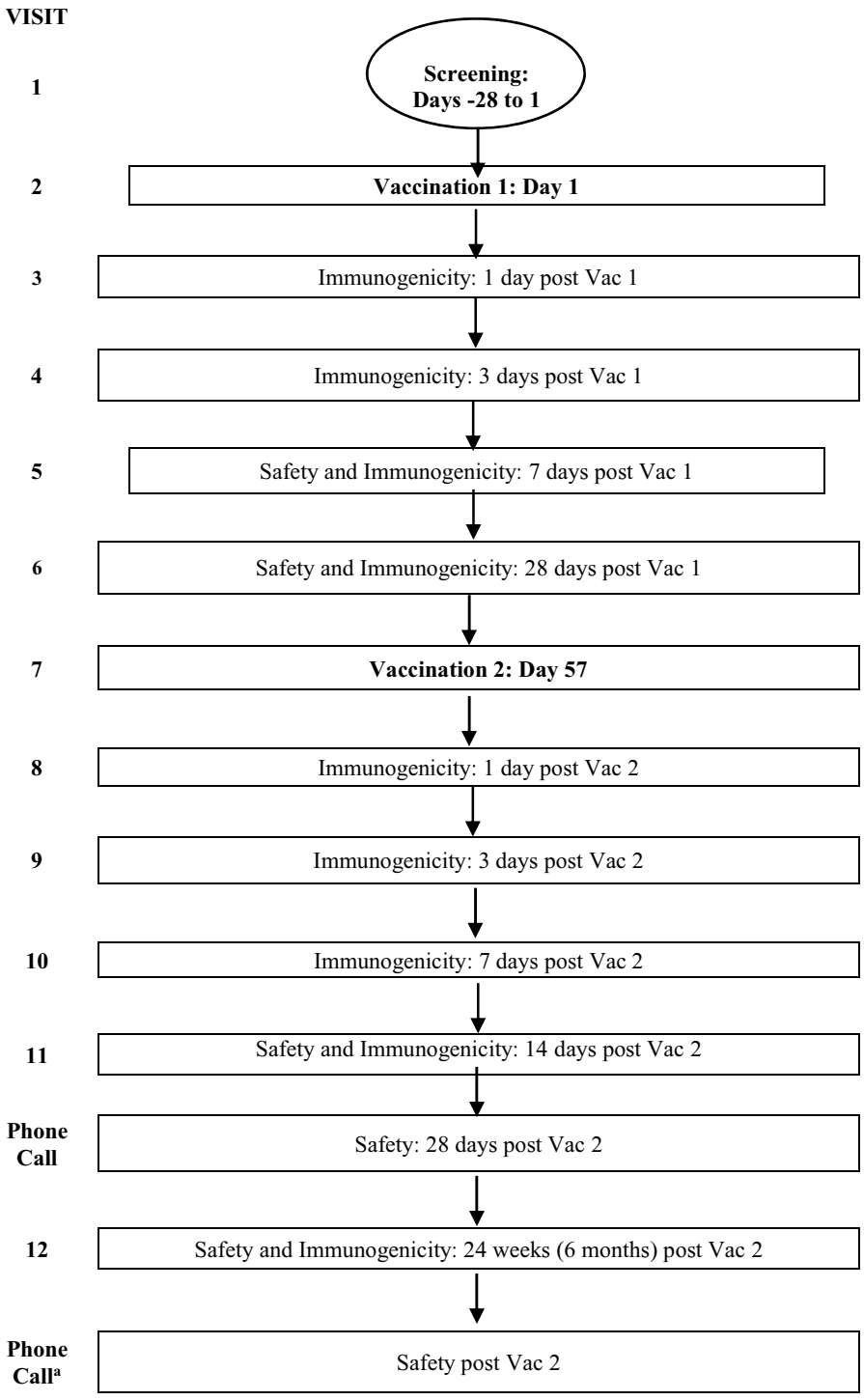
1.2. Schema for Participants in the Main Study

Figure 1: Schematic Overview



[a] For those participants who have already had their 6-month post Vac 2 visit (Visit 6) but have not yet reached 12-months post Vac 2. Note: those participants that had already reached their 1-year follow-up prior to implementation of Amendment 7 will also be included in the final analysis.

1.3. Schema for Participants in the Sub Study



[a] For those participants who have already had their 6-month post Vac 2 visit (Visit 6) but have not yet reached 12-months post Vac 2. Note: those participants that had already reached their 1-year follow-up prior to implementation of Amendment 7 will also be included in the final analysis.

1.4. Schedule of Activities (SoA)

1.4.1. 2-dose Vaccination Schedule for Participants in the Main Study

Phase	Screening[a]	Study Period[b]									
Clinic Visit #	**1**	**2**	**Phone Call[c]**	**3**	**4**	**Phone Call[c]**	**5**	**Phone Call[c]**	**6**	**Phone Call[d]**	**Exit[e]**
Visit Timing		**Vac 1**	**Post Vac 1 + 7 d**	**Post Vac 1 + 28 d**	**Vac 2**	**Post Vac 2 + 7 d**	**Post Vac 2 +14 d**	**Post Vac 2 + 28 d**	**Post Vac 2 + 24 w**		
Visit Day/Week	**-28 to 1**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 64***	**Day 71***	**Day 85***	**Week 32*** (6m post Vac 2)		
Visit Window			**±2 d**	**±3 d**	**-3/+7 d**	**±2 d**	**±3 d**	**±3 d**	**±21 d**	**+1 month**	
Visit Type	**Screening**	**Vaccine 1**	**Safety**	**Safety and Immuno**	**Vaccine 2**	**Safety**	**Safety and Immuno**	**Safety**	**Safety and Immuno**	**Safety**	
Written informed consent[f]	●										
Inclusion/exclusion criteria	●	●[1]									
Demographics	●										
Medical history/prestudy meds	●										
Physical examination[g]	●										
Vital signs[h] incl. body temperature	●	●[2]			●[2]						
Nasal swab sample and test for SARS CoV 2 RNA	●[6]	●[7]									
Serological test for anti SARS CoV 2 antibody (Local Laboratory)[i]	●[6][2 mL]										
Randomization		●[1]									
Prevaccination check[j]		●[1]			●[1]						
Urine pregnancy test[k]	●	●[1]			●[1]						
Humoral Immunity (serum), blood draw, mL[l]		●[1] 10		● 12	●[1] 10		● 10		● 10		●[3]10
Clinical lab blood draw (whole blood, plasma, serum), mL[m]		●[1] 15		●15	●[1] 15		●15				
SARS CoV 2 N Serology, mL (Central Laboratory)[n]				● 2.5			● 2.5				
Vaccination		●			●						
15 minutes post vaccination observation[o]		●			●						

Phase	Screening[a]	Study Period[b]									
Clinic Visit #	1	2	Phone Call[c]	3	4	Phone Call[c]	5	Phone Call[c]	6	Phone Call[d]	Exit[e]
Visit Timing		Vac 1	Post Vac 1 + 7 d	Post Vac 1 + 28 d	Vac 2	Post Vac 2 + 7 d	Post Vac 2 +14 d	Post Vac 2 + 28 d	Post Vac 2 + 24 w		
Visit Day/Week	-28 to 1	Day 1	Day 8	Day 29	Day 57	Day 64*	Day 71*	Day 85*	Week 32* (6m post Vac 2)		
Visit Window			±2 d	±3 d	-3/+7 d	±2 d	±3 d	±3 d	±21 d	+1 month	
Visit Type	Screening	Vaccine 1	Safety	Safety and Immuno	Vaccine 2	Safety	Safety and Immuno	Safety	Safety and Immuno	Safety	
Solicited AE recording		*- Continuous-*			*- Continuous-*						●[4]
Unsolicited AE recording[p]		*----- Continuous through +28 d-----*			*----- Continuous through +28 d-----*						●[5]
SAE/AESI recording[q]		*----------Continuous----------*									●
COVID 19 recording[r]		*----------Continuous----------*									●
MAAE recording[s]		*----------Continuous----------*									●
Concomitant meds[t]		*----------Continuous----------*									●
Participant diary distribution[u]		●			●						
Participant diary review[v]			●			●					
Approx. blood draw per day, mL:	2	25		29.5	25		27.5		10		10
Approx. cumulative blood draw, mL:	2	27		56.5	81.5		109		119		

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

*The phone call or these visits (including their window) are to be scheduled relative to the actual day of the previous vaccination, indicated as Visit Timing days/weeks post Vac 2.

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

b. If a participant shows COVID-19 like symptoms, the participant should contact the site for guidance and must follow their local country and site level recommendations for COVID-19.

c. The site will contact the participant 7 days post vaccination 1, 7-days post vaccination 2, and 28 days post vaccination 2 to enquire about compliance of patient diary completion that occurred between the actual vaccination visit and the current day.
d. Within 1 month, the site will contact any participants who have already had their 6-month post Vac 2 visit (Visit 6) but have not yet reached 12-months post Vac 2 for additional safety follow up.
e. For those participants who are unable to continue participation in the study up to Visit 7, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent from participation in the study will be offered an optional visit for safety follow-up. This includes the safety assessments of the early exit visit (no blood sampling for immunogenicity). If the participant does not want to receive the second vaccination, they can continue with other study procedures.
f. Signing of the ICF should be done before any study-related activity.
g. A history-directed physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
h. Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Heart rate and blood pressure measurements should be taken in the supine position and preceded by at least 5 minutes of rest. Vital signs measurements are recommended before blood sampling. Body temperatures will be measured preferably via the oral route.
i. The blood draw at screening will be used to determine serostatus by serological testing for eligibility in the main and sub study by a local laboratory.
j. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If any of these events occur within 24 hours prior to planned vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.
k. For women of childbearing potential only.
l. Serum collected can also be used for N-serology testing.
m. 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 stored for coagulation-related testing in a central laboratory, some of which will be conducted retrospectively (See Section 10.2, Appendix 2).
n. This blood draw occurs in the ongoing study for monitoring breakthrough infections and will be performed by a central laboratory.
o. Participants will be closely observed for a minimum of 15 minutes post vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 15 minutes post vaccination observation period is complete.
p. AEs and special reporting situations that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post vaccination.
q. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported for all participants from the moment of first vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).
r. At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing) 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. If the event occurs after 28 days, and it is not serious, it will be reported in the eCRF. The participant can continue in the study for safety follow-up if they choose to; however, this must be in accordance

with local country and site level recommendations for COVID-19 and they will not be permitted to receive further study vaccination administrations. (see Section 8.3.1).

s. MAAEs are to be reported for all participants from the moment of the 1st vaccination until 6 months after the last 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.

t. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of subsequent vaccination and for 28 days after the subsequent dose of study vaccine. Refer to Section 6.8 for collection and recording of concomitant therapies associated with SAEs, solicited and unsolicited AEs, suspected AESIs, and MAAEs. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.

u. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant. At Visit 4, the site is to report the 2nd vaccination date in the eCOA portal to ensure that the appropriate diary is visible in the electronic diary.

v. If an event is still ongoing on Day 8 or Day 64, the participant should continue to collect the information until resolution.

(S)AE = (serious) adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; MAAE = medically-attended adverse event; meds = medication; m = months; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; vac = vaccination; vp = virus particles.

1.4.2. 2-dose Vaccination Schedule for the Sub Study Participants

Phase	Screening[a]	Study Period[b]													
ClinicVisit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Phone Call**	**12**	**Phone Call[d]**	**Exit[e]**
Visit Timing		**Vac 1**	**Post Vac 1 + 1 d****	**Post Vac 1 + 3 d****	**Post Vac 1 + 7 d**	**Post Vac 1 + 28 d**	**Vac 2**	**Post Vac 2 + 1 d****	**Post Vac 2 + 3 d****	**Post Vac 2 + 7 d**	**Post Vac 2 +14 d**	**Post Vac 2 + 28 d**	**Post Vac 2 + 24 w**		
Visit Day/Week	**-28 to 1**	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 29**	**Day 57**	**Day 58**	**Day 60**	**Day 64***	**Day 71***	**Day 85*[c]**	**Week 32*** (6m post Vac 2)		
Visit Window					**±2 d**	**±3 d**	**-3/+7 d**			**±2 d**	**±3 d**	**±3 d**	**±21 d**	**+1 month**	
Visit Type	**Screening**	**Vaccine 1**	**Immuno**	**Immuno**	**[Safety and Immuno]**	**Safety and Immuno**	**Vaccine 2**	**Immuno**	**Immuno**	**Safety and Immuno**	**Safety and Immuno**	**Safety**	**Safety and immuno**	**Safety**	
Written informed consent[f]	●														
Inclusion/exclusion criteria	●	●[1]													
Demographics	●														
Medical history/prestudy meds	●														
Physical examination[g]	●														
Vital signs[h] incl. body temperature	●	●[2]					●[2]								
Nasal swab sample and test for SARS CoV 2 RNA	●[6]	●[7]													
Serological test for anti SARS CoV 2 antibody[i] (Local Laboratory)	●[6][2 mL]														
Randomization		●[1]													
Prevaccination check[j]		●[1]					●[1]								
Urine pregnancy test[k]	●	●[1]					●[1]								
Humoral Immunity (serum), blood draw, mL[l]		●[1] 10				● 12	●[1] 10				● 10		● 10		●[3]10

Phase	Screening[a]	Study Period[b]													
ClinicVisit #	1	2	3	4	5	6	7	8	9	10	11	Phone Call	12	Phone Call[d]	Exit[e]
Visit Timing		Vac 1	Post Vac 1 + 1 d**	Post Vac 1 + 3 d**	Post Vac 1 + 7 d	Post Vac 1 + 28 d	Vac 2	Post Vac 2 + 1 d**	Post Vac 2 + 3 d**	Post Vac 2 + 7 d	Post Vac 2 +14 d	Post Vac 2 + 28 d	Post Vac 2 + 24 w		
Visit Day/Week	-28 to 1	Day 1	Day 2	Day 4	Day 8	Day 29	Day 57	Day 58	Day 60	Day 64*	Day 71*	Day 85*[c]	Week 32* (6m post Vac 2)		
Visit Window					±2 d	±3 d	-3/+7 d			±2 d	±3 d	±3 d	±21 d	+1 month	
Visit Type	Screening	Vaccine 1	Immuno	Immuno	[Safety and Immuno]	Safety and Immuno	Vaccine 2	Immuno	Immuno	Safety and Immuno	Safety and Immuno	Safety	Safety and immuno	Safety	
Clinical lab blood sample (whole blood, plasma, serum), mL[m]		●[1] 15				●15	●[1] 15				●15				
SARS CoV 2 N Serology, mL[n] (Central Laboratory)						● 2.5					● 2.5				
Innate MoA Serum, mL		●[1] 3.0	● 3.0	● 3.0	● 3.0		●[1] 3.0	● 3.0	● 3.0	● 3.0					
Innate MoA PaxGene, mL		●[1] 2.5	● 2.5	● 2.5	● 2 5		●[1] 2.5	● 2.5	● 2.5	● 2.5					
Vaccination		●					●								
15 minutes post vaccination observation[o]		●					●								
Solicited AE recording		*- Continuous-*					*- Continuous-*								●[4]
Unsolicited AE recording[p]		*- - - - - Continuous through +28 d- - - - -*					*- - - - - Continuous through +28 d- - - - -*								●[5]
SAE/AESI recording[q]		*- - - - - Continuous- - - - -*													●
COVID 19 recording[r]		*- - - - - Continuous- - - - -*													●
MAAE recording[s]		*- - - - - Continuous- - - - -*													●
Concomitant meds[t]		*- - - - - Continuous- - - - -*													●

Phase	Screening[a]	Study Period[b]													
ClinicVisit #	1	2	3	4	5	6	7	8	9	10	11	Phone Call	12	Phone Call[d]	Exit[e]
Visit Timing		Vac 1	Post Vac 1 + 1 d**	Post Vac 1 + 3 d**	Post Vac 1 + 7 d	Post Vac 1 + 28 d	Vac 2	Post Vac 2 + 1 d**	Post Vac 2 + 3 d**	Post Vac 2 + 7 d	Post Vac 2 +14 d	Post Vac 2 + 28 d	Post Vac 2 + 24 w		
Visit Day/Week	-28 to 1	Day 1	Day 2	Day 4	Day 8	Day 29	Day 57	Day 58	Day 60	Day 64*	Day 71*	Day 85*[c]	Week 32* (6m post Vac 2)		
Visit Window					±2 d	±3 d	-3/+7 d			±2 d	±3 d	±3 d	±21 d	+1 month	
Visit Type	Screening	Vaccine 1	Immuno	Immuno	[Safety and Immuno]	Safety and Immuno	Vaccine 2	Immuno	Immuno	Safety and Immuno	Safety and Immuno	Safety	Safety and immuno	Safety	
Participant diary distribution[u]		●					●								
Participant diary review[v]					●					●					
Approx. blood draw per day, mL:	2	30.5	5.5	5.5	5.5	29.5	30.5	5.5	5.5	5.5	27.5		10		10
Approx. cumulative blood draw, mL:	2	32.5	38	43.5	49	78.5	109	114.5	120	125.5	153		163		

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

*The phone call or these visits (including their window) are to be scheduled relative to the actual day of the previous vaccination, indicated as Visit Timing days/weeks post Vac 2.

a. Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide on Day 1. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination.
b. If a participant shows COVID-19 like symptoms, the participant should contact the site for guidance and must follow their local country and site level recommendations for COVID-19.
c. The site will contact the participant 28 days post vaccination 2 to enquire about compliance of patient diary completion that occurred between the actual vaccination visit and the current day.
d. Within 1 month, the site will contact any participants who have already had their 6-month post Vac 2 visit (Visit 6) but have not yet reached 12-months post Vac 2 for additional safety follow up.
e. For those participants who are unable to continue participation in the study up to Visit 13, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. Participants who wish to withdraw consent from participation in the study will be offered an optional visit for safety follow-up. This

includes the safety assessments of the early exit visit (no blood sampling for immunogenicity). If the participant does not want to receive the second vaccination, they can continue with other study procedures.

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

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

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

i. The blood draw at screening will be used to determine serostatus by serological testing for eligibility in the sub study by a local laboratory.

j. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If any of these events occur within 24 hours prior to planned vaccination, the vaccination can be rescheduled as long as this is in agreement with the allowed windows. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance. The investigator should also check if any other reasons, as listed in Section 7.1, Discontinuation of Study Vaccination, have been met and would prevent further study vaccination.

k. For women of childbearing potential only.

l. Serum collected can also be used for N-serology testing.

m. 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 stored for coagulation-related testing in a central laboratory, some of which will be conducted retrospectively (See Section 10.2, Appendix 2).

n. This blood draw occurs in the ongoing study for monitoring breakthrough infections and will be performed by a central laboratory.

o. Participants will be closely observed for a minimum of 15 minutes post vaccination. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study site personnel following this observation period and participants will be allowed to leave the study site after it is documented that the 15 minutes post vaccination observation period is complete.

p. AEs and special reporting situations that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other unsolicited AEs and special reporting situations will be reported for each vaccination from the time of vaccination until 28 days post vaccination.

q. All SAEs related to study procedures or non-investigational sponsor products will be reported for all participants from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported for all participants from the moment of first vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure (see Section 8.3.1).

r. At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing) 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. If the event occurs after 28 days, and it is not serious, it will be reported in the eCRF. The participant can continue in the study for safety follow-up if they choose to; however, this must be in accordance with local country and site level recommendations for COVID-19 and they will not be permitted to receive further study vaccination administrations. (see Section 8.3.1).

s. MAAEs are to be reported for all participants from the moment of the 1st vaccination until 6 months after the last 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.

t. Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations must be recorded from the first dose of study vaccine until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of subsequent vaccination and for 28 days after the subsequent dose of study vaccine. Refer to Section 6.8 for collection and recording of concomitant therapies associated with SAEs,

solicited and unsolicited AEs, suspected AESIs, and MAAEs. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 8.3.1.

u. At Visit 2, in addition to the diary, a ruler and thermometer will be distributed to each participant. At Visit 7, the site is to report the 2nd vaccination date in the eCOA portal to ensure that the appropriate diary is visible in the electronic diary.

v. If an event is still ongoing on Day 8 or Day 64, the participant should continue to collect the information until resolution.

(S)AE = (serious) adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; d = day(s); ICF = informed consent form; MAAE = medically-attended adverse event; meds = medication; m = months; MoA= mechanism of action; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; TTS= thrombosis with thrombocytopenia syndrome; vac = vaccination; vp = virus particles.

1.4.3. Participants with a Suspected AESI

The medical management of thrombotic events with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg. from the American Society of Hematology [American Society of Hematology 2021], British Society of Haematology - Expert Haematology Panel [British Society for Haematology. Guidance 2021], and the CDC [CDC 2021]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Management of the participant should not be delayed by decision-making of the Janssen Adjudication Committee.

In the event of a suspected thrombotic event or TTS, laboratory assessments (to be performed locally) 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 lab blood sample (whole blood), mL[d]	● 15	● 15
TTS AESI form[e]	*---Continuous---*	
Concomitant therapies[f]	●	●

a. Day 1 refers to first awareness of the event, which might be later than the date of onset. Every effort should be made to report as much information as possible about the event to the sponsor in a reasonable timeframe. The investigator should contact the sponsor for input on the feasibility of collecting blood samples, including the need for additional samples based on the nature of the event.
b. Day 29 is to be calculated relative to the actual day of onset of the event. If the event is not resolved on Day 29, subsequent follow-up assessments can be performed at unscheduled visits as needed until resolution of the event.
c. Suspected AESIs must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) or causality assessment (see Section 8.3.6).
d. Whole blood samples will be used for a platelet count (as part of a complete blood count, if applicable) in a local laboratory or substitute for local laboratory, depending on local feasibility towards turnaround time of sample processing. Serum and plasma samples will be used for coagulation-related testing in a central laboratory (See Section 10.2, Appendix 2). For the follow-up visit, the volume of blood to be collected may vary depending on the clinical evaluation of the case.
e. Medical information on local case management will be collected. Upon becoming aware of the suspected AESI, study site personnel should provide information on an ongoing basis. See Section 8.3.6 and Section 10.8, Appendix 8 for further details.
f. Refer to Section 6.8 for collection and recording of concomitant therapies associated with a suspected AESI.

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

2. INTRODUCTION

Ad26.COV2.S (also known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein, stabilized in its prefusion conformation, which will be assessed in this study.

For the most comprehensive nonclinical and clinical information regarding Ad26.COV2.S, refer to the IB, Edition 6.0 (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 as defined in Section 6.2. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject".

Study VAC31518COV3003 is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V).

COVID-19 Vaccine and Considerations

Currently, there is only limited availability of licensed/authorized vaccines for the prevention of coronavirus disease-2019 (COVID-19). The continued development of safe and effective vaccines is considered critical to contain the current outbreak and help prevent future outbreaks.

Although the quantitative correlate of protection against SARS-CoV-2 infection has not yet been identified, neutralizing antibody responses against the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) S protein have been associated with protection against experimental SARS-CoV and MERS-CoV infection in nonclinical models (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 adenoviral vaccine (AdVac®) vector platform, developed by Crucell Holland B.V. (now Janssen Vaccines & Prevention B.V.) allows for high-yield production of replication-incompetent adenovirus vectors, eg, Ad26, with desired inserts. The adenovirus E1 region is deleted to render the vector replication-incompetent and create space for transgenes, with viral replication taking place in cells that complement for the E1 deletion in the virus genome.

Ad26 has been selected as a potential vaccine vector because there is substantial nonclinical and clinical experience with Ad26-based vaccines that demonstrate their capacity to elicit strong humoral and cellular immune responses and their acceptable safety profile, irrespective of the antigen transgene (see also Section 2.3.1).

The immunogenicity profile of adenoviral vectors is illustrated by data obtained following the immunization of adults with Ad26-vectored human immunodeficiency virus (HIV) vaccines (Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV), an Ad26-vectored Ebola virus vaccine (Ad26.ZEBOV), Ad26-vectored respiratory syncytial virus (RSV) vaccines (Ad26.RSV.FA2 and Ad26.RSV.preF), an Ad26-vectored Zika virus vaccine (Ad26.ZIKV.001), and an Ad26-vectored malaria vaccine (Ad26.CS.01). Antigen-specific antibody responses are observed in almost all participants after 1 dose, in both naïve and pre-immune individuals (RSV). These antibodies may persist for a year or more (RSV) after a single vaccination in pre-immune participants. They have functional properties of neutralization (RSV, Zika), crystallizable fragment (Fc)-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (HIV, malaria). Furthermore, these data support an immunogenicity profile with emphasis on T-helper cell type 1 (Th)1 responses and demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in cluster of differentiation (CD) 4^+ and $CD8^+$ T cells (Barouch 2013, Milligan 2016, 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 (Zhou 2004).

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 (Li 2020). Early epidemiological investigations suggested that the majority of early cases were linked to a seafood market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts (Li 2020). However, there is some controversy about the initial origin of the virus (Cyranoski 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 2005a). 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).

SARS-CoV-2 has spread rapidly and globally since its emergence. The WHO declared that the outbreak constituted a public health emergency of international concern on January 30, 2020 and declared the outbreak to be a pandemic on March 11, 2020 (WHO 2005a, WHO 2020c). As of December 11th, 2020, approximately 69,688,577 cases of COVID-19 and approximately 1,584,063 COVID-19-related deaths have been reported (Johns Hopkins CSSE 2020).

Symptoms of infection may appear from 2 to 14 days following exposure, with the clinical manifestations ranging from mild symptoms to severe illness or death (CDC 2020b). Severe clinical presentations have been reported in as many as 20% to 25% of laboratory-confirmed cases (ECDC 2020b). In a study of 99 patients in a single center in Wuhan with SARS-CoV-2 infection confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), the most commonly reported clinical manifestations were fever (83%), cough (82%), shortness of breath (31%), and muscle aches (11%) (Chen 2020). In chest X-rays and computed tomographic (CT) scans, 75% of patients showed bilateral pneumonia and 14% of patients showed diffuse mottling and ground-glass opacities. In a further study of 138 patients with novel coronavirus-induced pneumonia in a single center in Wuhan, common symptoms included fever (98.6%), fatigue (69.6%), and dry cough (59.4%) (US Dept Health 1998). Lymphopenia occurred in 70.3% of patients, and chest CT scans showed bilateral patchy shadows or ground-glass opacities in the lungs of all patients. Thirty-six patients (26%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome, arrhythmia, and shock. Subsequent US Centers for Disease Control and Prevention (CDC) descriptions of COVID-19 clinical case definitions and Janssen-sponsored interviews with COVID-19-experienced clinicians have included signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis (DVT), Kawasaki-like disease, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others.

The identification of SARS-CoV-2 follows the emergence of 2 other novel betacoronaviruses capable of causing severe human disease over the past 18 years: SARS-CoV and MERS-CoV, which have nucleotide sequence identity with SARS-CoV-2 of approximately 79% and 50%, respectively (Lu 2020). The first known cases of SARS occurred in Southern China in November 2002 (WHO 2004). The etiological agent, SARS-CoV, is believed to be an animal virus that crossed the species barrier to humans followed by human-to-human transmission, leading to SARS cases in >25 countries. The MERS-CoV was isolated from a patient in Saudi Arabia who died of severe pneumonia and multi-organ failure in June 2012 (Zumla 2016). MERS-CoV is considered to be a zoonotic virus capable of nonsustained human-to-human transmission. Since 2012, sporadic cases and community and health-care-associated clusters of infected individuals have been reported in the Middle East.

Patients with SARS or MERS present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations (Chan 2015, Zumla 2016). Both diseases have predominantly respiratory manifestations, but extrapulmonary features may occur in severe cases. By July 2003, the international spread of SARS-CoV resulted in 8,098 SARS cases and 774 deaths (case-fatality rate: 10%) with substantial social, economic and health service disruption in some affected countries (Chan 2015, WHO 2004). The case-fatality rate of MERS-CoV infections is estimated to be 35% (Chan 2015).

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

The sponsor is developing a COVID-19 vaccine based on a human replication-incompetent Ad26 vector encoding the SARS-CoV-2 S protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate coronavirus vaccines against SARS-CoV (2002-2003 outbreak), and the common conclusion that has emerged from the evaluation of several different vaccines is that the viral S protein is the only significant target for neutralizing antibodies (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.

2.1. Study Rationale

Detailed information about the rationale for the selected dose for the release titer ($5x10^{10}$ vp) can be found in Section 4.3.

The purpose of this study is to aid in the establishment of end-expiry specifications for the 1-dose and 2-dose vaccine regimens being assessed in the Phase 3 efficacy studies VAC31518COV3001 and VAC31518COV3009, respectively. The lower dose ($3.5\ x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) levels mimic vaccine degradation to enable determination of product expiry. In order to increase the end of shelf life specifications a potential target release titer of $7x10^{10}$ vp will be evaluated. A higher titer of $9x10^{10}$ vp will also be evaluated as is the upper limit of the release range (potential maximum vp at release). For this study's purpose 6 dose levels of Ad26.COV2.S will be assessed: $9x10^{10}$ vp, $7x10^{10}$ vp, $5x10^{10}$ vp (release titer), $3.5x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp. The following NI comparisons by sequential approach will be performed:

1-dose $9x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

If the above is demonstrated, then:

1-dose $2.5x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

1-dose $7x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

If the above is demonstrated, then:

1-dose $3.5x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

If the above is demonstrated, then:

1-dose $1.25x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

To demonstrate the following in sequential order:

2-doses $9x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

2-doses $9x10^{10}$ vp Ad26.COV2.S compared to 2-doses $5x10^{10}$ vp Ad26.COV2.S

2-doses $2.5x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

2-doses $2.5x10^{10}$ vp Ad26.COV2.S compared to 2-doses $5x10^{10}$ vp Ad26.COV2.S

2-doses $7x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

2-doses $7x10^{10}$ vp Ad26.COV2.S compared to 2-doses $5x10^{10}$ vp Ad26.COV2.S

2-doses $3.5x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

2-doses $3.5x10^{10}$ vp Ad26.COV2.S compared to 2-doses $5x10^{10}$ vp Ad26.COV2.S

2-doses $1.25x10^{10}$ vp Ad26.COV2.S compared to 1-dose $5x10^{10}$ vp Ad26.COV2.S

2-doses $1.25x10^{10}$ vp Ad26.COV2.S compared to 2-doses $5x10^{10}$ vp Ad26.COV2.S

Prior to the start of the VAC31518COV3001 and VAC31518COV3009 studies, the Phase 1 and 2 studies VAC31518COV1001 and VAC31518COV2001 were initiated to assess several dose levels of the vaccine including $1x10^{11}$ vp, $5x10^{10}$ vp, $2.5x10^{10}$ vp and $1.25\ x10^{10}$ vp.

2.2. Background

Nonclinical Pharmacology

Nonclinical studies were performed to test the immunogenicity of different vaccine candidates, leading to the selection of the current vaccine for this development program. In addition, vaccine efficacy of Ad26.COV2.S has been shown in Syrian hamsters and NHP. Details are provided in the IB (IB Ad26.COV2.S. 2022).

Nonclinical Safety

Biodistribution

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

Toxicology

The sponsor has significant nonclinical experience with Ad26-vectored vaccines using various transgenes encoding HIV, RSV, Ebola virus, filovirus, human papilloma virus, Zika, influenza (universal flu [Uniflu]), and malaria antigens. To date, more than 10 Good Laboratory Practice (GLP) combined repeated dose toxicology and local tolerance studies have been performed in rabbits (and 1 study in rats), testing the nonclinical safety of various homologous and heterologous regimens with Ad26-based vaccines at full human dose levels up to 1.2×10^{11} vp. No adverse effects have been observed in these studies. The vaccine-related effects observed were similar across studies, considered to be reflective of a physiological response to the vaccines administered, and seem to be independent of the antigen transgene. Overall, there were no safety signals detected in any of the available GLP toxicology studies with Ad26-based vaccines up to the highest dose level tested (1.2×10^{11} vp). In a combined embryo-fetal and pre- and postnatal development GLP study in female rabbits with another Ad26-based vaccine (Ad26.ZEBOV, encoding an Ebola virus antigen), there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A repeated dose and local tolerance GLP study, and a combined embryo-fetal and pre- and postnatal development GLP study with Ad26.COV2.S are planned to run in parallel with study VAC31518COV1001.

Clinical Studies

At the start of this study, the safety and immunogenicity (post-Dose 1) of Ad26.COV2.S, administered at several dose levels, has been demonstrated in healthy adults in the first-in-human study VAC31518COV1001 (IB Ad26.COV2.S 2022, Sadoff 2020) and is currently further evaluated in Phase 2 study VAC31518COV2001. Based on the interim data of study VAC31518COV1001, 2 clinical studies have been initiated to assess the protective efficacy of Ad26.COV2.S at the $5x10^{10}$vp dose level, administered either as a 1-dose (study VAC31518COV3001) or as a 2-dose schedule (study VAC31518COV3009).

Refer to the IB for a high level description of all ongoing studies with Ad26.COV2.S (IB Ad26.COV2.S 2022).

Clinical Safety Experience With Ad26-based Vaccines

As described above, replication-incompetent Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus and filovirus, and has been used in the now licensed Ebola virus vaccine (Zabdeno/Ad26.ZEBOV).

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

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

As of 04 September 2020, more than 109,000 participants were enrolled in ongoing studies and in the ongoing immunization campaign in Rwanda (UMURINZI Ebola Vaccine Program campaign). However, their safety data were not included in the AdVac® safety database report V5.0 because the studies were still blinded, the studies were unblinded but their analysis took place after the AdVac® safety database report cut-off date, or the study data were not integrated in the Ad26- based vaccine database used for the report.

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

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 T-helper cell (Th) type 2-skewed type T-cell response (Moghaddam 2006).

Vaccine-induced ERD has also been described for SARS-CoV and MERS-CoV in some animal models in which candidate vaccines induced a Th2 biased immune response (Agrawal 2016, Bolles 2011, Deming 2006, Honda-okubo 2015, Houser 2017, Smatti 2018) but proof of human SARS-CoV or MERS-CoV vaccine-associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. For SARS and MERS, the mechanism of enhanced disease observed in mice has been associated with a Th2-mediated eosinophilic infiltration in the lung, which is reminiscent of ERD effects observed after RSV infection of mice immunized with FI-RSV. Similar to RSV vaccines, enhanced disease has been shown for whole-inactivated SARS-CoV vaccines, as well as subunit vaccines inducing a Th2-type immune response, which can be rescued by formulating vaccines in Th1-skewing adjuvants. In addition to a Th1-biased immune response, also induction of a high proportion of neutralizing antibodies compared with virus binding antibodies is desirable to prevent predisposition to enhanced disease as observed for RSV vaccines. While vaccine-associated enhanced disease was observed in nonclinical studies with experimental SARS and MERS vaccines, it is not a given that the same risk applies to COVID-19 vaccines To the sponsor's knowledge, antibody-related COVID-19 disease enhancement has not been observed in nonclinical models yet. Antibodies against the receptor binding domain of SARS-CoV-2 were shown not to enhance in vitro infectivity. Repeated SARS-CoV-2 challenge of NHP or NHP studies with Th2 biasing COVID-19 vaccines that would be expected to predispose to enhanced disease did not show any signs of enhanced disease. In addition, disease enhancement was not observed in NHP immunized with ChAdOx1 encoding SARS-CoV-2 S protein prior to challenge with SARS-CoV-2 (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 202, Milligan 2016, Mutua 2019, Salisch 2019, Stephenson 2020, van der Fits 2020, Widjojoatmodjo 2015, Zhan 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.Mos4.HIV) and Ad26-vectored Ebola vaccine (Ad26.ZEBOV). These data show predominantly IFNγ and TNFα production in $CD4^+$ and $CD8^+$ T cells (Anywaine 2019, Barouch 2013, Barouch 2018). In the RSV vaccine clinical development program, Ad26.RSV.preF was evaluated in healthy RSV- seropositive toddlers aged 12 to 24 months (Phase 1/2a study VAC18194RSV2001). Safety data from the primary analysis at 28 days after the second study vaccination revealed no safety concerns following Ad26.RSV.preF dosing at 5×10^{10} vp or a placebo. The immunogenicity of a single immunization with Ad26.RSV.preF in RSV-seropositive toddlers aged 12 to 24 months, including a favorable Th1 bias, was confirmed. In August 2020, the study had been completed and showed that Ad26.RSV.preF had an acceptable safety and reactogenicity profile. In a further study of Ad26.RSV.preF in RSV-seronegative toddlers aged 12 to 24 months (Phase 1/2a study VAC18194RSV2002), initial safety data have not revealed concerns after Ad26.RSV.preF vaccination.

In Study COV1001, Ad26.COV2.S induced cellular immune responses were assessed by ICS and ELISpot. Robust CD4+ T and CD8+ T-cell responses were seen following a single vaccination

with 5×10^{10} vp or 1×10^{11} vp. 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) in all participants with a positive CD4+ T-cell response (IB Ad26.COV2.S. 2022).

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.COV2.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 start of this study, the post-dose 1 safety and reactogenicity profiles of Ad26.COV2.S ($5x10^{10}$ and $1x10^{11}$ 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 1] and ≥65 years of age [Cohort 3]) in the first-in-human study VAC31518COV1001 (Sadoff 2020). Local adverse events were observed in 58% and 27% of participants in Cohorts 1a and 3, respectively. Solicited systemic adverse events were reported in 64% and 36% of participants in Cohorts 1 and 3, respectively. Fevers occurred in 19% (5% Grade 3) and 4% (0% Grade 3) of participants of Cohorts 1 and 3, respectively, were mostly mild or moderate, and resolved within 1 to 2 days after vaccination. The most frequent local adverse event was injection site pain and the most frequent solicited adverse events were fatigue, headache and myalgia. The safety and reactogenicity profiles of 2 dose levels, $5x10^{10}$ and $1x10^{11}$ vp were considered acceptable.

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

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

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

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. These cases occurred approximately 1-2 weeks following vaccination, mostly in women under 60 years of age. Thrombosis in combination with thrombocytopenia can be fatal. The exact physiology of TTS is unclear. TTS is considered an important identified risk for Ad26.COV2.S. Participants should be instructed to seek

immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, skin bruising and/or petechiae beyond the site of vaccination. The medical management of thrombosis with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, from the American Society of Hematology [American Society of Hematology. COVID-19 resources 2021], British Society of Haematology - Expert Haematology Panel [British Society for Haematology. Guidance produced from the Expert Haematology Panel 2021] and the CDC [CDC 2021]). 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), which may facilitate diagnosis and clinical management of the event. Reports of adverse events following use of the Ad26.COV2.S Vaccine under emergency use authorization (EUA) suggest 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.

Heparin-induced Immune Thrombotic Thrombocytopenia

TTS has been found to resemble heparin-induced thrombocytopenia with thrombosis (HITT), which is mediated by antibodies against complexes of heparin and platelet factor 4 (PF4) that induce Fc receptor-mediated activation of platelets and hypercoagulation (Arepally 2021). Current evidence suggests that these 2 conditions may be linked (Streiff 2021). The exact mechanisms remain to be investigated, but anti-PF4 antibodies are suspected to be involved in the pathogenesis of TTS associated with vaccination.

Risks Related to Adenoviral-vectored Vaccines

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

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

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

In adults, the most frequently reported solicited local AE was injection site pain (56.9% of Ad26 participants, compared with 22.5% of placebo participants). All other solicited local AEs were experienced by less than 25% of adult participants. The most frequently experienced solicited local AE in children was injection site pain, reported in 13.9% of children aged 1-3 years, 29.8% of children aged 4-11 years, and 24.8% of children aged 12-17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4-11 years and 14.3% in children aged 12-17 years. No children aged 1-3 years have received placebo.

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

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

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

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

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

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

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

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

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with intramuscular injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term. Instructions regarding use of antipyretic medication can be found in Section 6.8.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops,

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

participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

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

After each vaccination, participants will remain at the study site for at least 15 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

Pregnancy and Birth Control

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

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

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

Risks from Blood Draws

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

Risks from Collection of Nasal Swabs

Collection of a nasal swab may cause a nosebleed. Assistance with the collection of nasal swab samples bears the risk of potentially infecting the assistant.

Theoretical Risk of Enhanced Disease

Vaccine-associated enhanced disease has been described for SARS-CoV and MERS-CoV in some animal models (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). Participants in the present study will be informed of the theoretical risk of disease enhancement in the ICF.

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 for Study Participation

Participants may benefit from clinical testing and physical examination.

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

2.3.3. Benefit-Risk Assessment for 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 (SoA).

  After each vaccination, participants will remain at the study site for at least 15 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited signs and symptoms. Details are provided in Section 8.3.

  The investigator or the designee will document unsolicited adverse events, SAEs and MAAEs as indicated in Sections 8.3 and 10.4.

  TTS is considered to be an AESI (Section 8.3.6). Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/µL (Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome 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 1.4.3.

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

A program IDMC has been established to monitor safety data on an ongoing basis in specific studies. This committee will be provided with relevant safety data from this study, such as SAEs, that will help the IDMC to have an overall view of the safety profile of the vaccine. Additional ad hoc reviews may be performed further to the occurrence of any SAE, or at the request of the IDMC or 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 on Day 1.

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

  Contraindications to vaccination are included in Section 5.5.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES AND ENDPOINTS FOR PARTICIPANTS IN THE MAIN STUDY

Objectives	Endpoints
Primary	
To demonstrate non-inferiority (NI) in the following sequential order: • NI after 1-dose of Ad26.COV2.S $9x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $2.5x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $7x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1 dose of Ad26.COV2.S $3.5x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 1-dose of Ad26.COV2.S $1.25x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)	• Binding antibody concentrations to SARS-CoV-2 S protein as measured by ELISA 28 days after vaccination • NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 28 days post-dose 1, using a NI margin of 2/3 for the GMC ratio (GMC $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp/GMC $5x10^{10}$ vp)

Objectives	Endpoints
To demonstrate NI in the following sequential order: • NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp vs 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp vs 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $7x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $7x10^{10}$ vp vs 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $3.5x10^{10}$ vp vs 1 dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $3.5x10^{10}$ vp vs 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S $1.25x10^{10}$ vp vs 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer) • NI after 2-doses of Ad26.COV2.S 1.25x1010 vp vs 2-doses of Ad26.COV2.S 5x1010 vp (release titer)	• Binding antibody concentrations to SARS-CoV-2 S protein as measured by ELISA 14 days after vaccination 2 • NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 14 days post-dose 2 ($9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp) and 28 days post-dose 1 or 14 days post-dose 2 ($5x10^{10}$ vp), using a NI margin of 2/3 for the GMC ratio (GMC [$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp)/GMC $5x10^{10}$ vp)
Secondary	
To assess the humoral immune response and durability to Ad26.COV2.S across all groups, at all blood collection timepoints.	• Serological response to vaccination and binding antibody GMCs to SARS.COV-2 S protein as measured by ELISA, or equivalent assay
To assess the safety and reactogenicity of Ad26.COV2.S administered at several dose levels.	• Solicited local and systemic AEs for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • SAEs throughout the study (from first vaccination until end of the study)

Objectives	Endpoints
	• Adverse events of special interest (AESIs [from first vaccination until end of the study]) • MAAEs (until 6 months post-dose 2) • AEs leading to study discontinuation (during the entire study) for all participants following vaccination
Exploratory	
To further explore humoral immune responses to Ad26.COV2.S across all groups at all or selected blood collection timepoints.	Exploratory analyses may include the following: • SARS-CoV-2 neutralization as assessed by SARS-CoV-2 neutralization assays VNA (wtVNA and/or psVNA) including neutralization of emerging SARS-CoV-2 variants • SARS-CoV-2 binding antibodies against emerging SARS-CoV-2 variants as assessed by S-ELISA or equivalent assay • Adenovirus neutralization • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass and IgG isotype • Analysis of circulating Spike protein • 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
To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints
To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of participants with positive non-S protein ELISA or equivalent assay (eg, nucleocapsid [N] protein ELISA)

Objectives	Endpoints
To examine the immune response in vaccinated individuals with prior or breakthrough infection.	• SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein
To assess hematology laboratory parameters before and after Ad26.COV2.S administration.	• Including but not limited to: Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers, and anti-PF4

GMC=geometric mean concentration

OBJECTIVES AND ENDPOINTS FOR PARTICIPANTS IN THE SUB STUDY

Objectives	Endpoints
Secondary	
To assess the humoral immune response and durability to Ad26.COV2.S across all groups in the sub study, at all blood collection timepoints.	• Serological response to vaccination and binding antibody GMCs to SARS.COV-2 S protein as measured by ELISA, or equivalent assay
To assess the safety and reactogenicity of Ad26.COV2.S administered at several dose levels.	• Solicited local and systemic AEs for 7 days after each vaccination • Unsolicited AEs for 28 days after each vaccination • SAEs throughout the study (from first vaccination until end of the study) • Adverse events of special interest (AESIs [from first vaccination until end of the study]) • MAAEs (until 6 months post-dose 2)
Exploratory	
To further explore humoral immune responses to Ad26.COV2.S across all groups in the sub study at all or selected blood collection timepoints.	Exploratory analyses may include the following: • SARS-CoV-2 neutralization as assessed by SARS-CoV-2 neutralization assays VNA (wtVNA and/or psVNA) including neutralization of emerging SARS-CoV-2 variants • SARS-CoV-2 binding antibodies against emerging SARS-CoV-2 variants as assessed by S-ELISA or equivalent assay • Adenovirus neutralization • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass and IgG isotype • Analysis of circulating Spike protein • 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
To assess the correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2, in a subset of participants at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints

Objectives	Endpoints
To assess for the occurrence of asymptomatic SARS-CoV-2 infection.	• The number of participants with positive non-S protein ELISA or equivalent assay (eg, nucleocapsid [N] protein ELISA)
To examine the immune response in vaccinated individuals with prior or breakthrough infection	• SARS-CoV-2 neutralizing titers in serum measured by a VNA (wild-type virus and/or pseudovirion expressing S protein) • SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S protein
To evaluate the innate, pro-inflammatory and other potentially relevant responses to Ad26.COV2.S vaccination at selected timepoints.	• Analysis of messenger ribonucleic acid (mRNA) expression levels of vaccine-induced innate responses including inflammatory and coagulation-related mediators • Analysis of cytokines, chemokines, and other protein- or lipid mediators of the innate immune response.
To assess hematology laboratory parameters before and after Ad26.COV2.S administration.	• Including but not limited to: Lupus anticoagulants, anti-β2 glycoprotein, anti-cardiolipin, D-dimers, and anti-PF4

Ad26=adenovirus 26; GMC=geometric mean concentration

If a correlate or threshold for protection against COVID-19 is established in terms of humoral immunity, then a statistical comparison to that correlate or threshold will substitute non-inferiority testing to immune responses to vaccine at release, as outlined in a revised analytical plan.

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

HYPOTHESES

Formal non-inferiority (NI) testing will be applied to demonstrate NI of 1-dose and 2-doses of 9×10^{10} vp, $2.5\text{x}10^{10}$ vp , 7×10^{10} vp, $3.5\text{x}10^{10}$ vp, and $1.25\text{x}10^{10}$ vp Ad26.COV2.S versus 1-dose and 2-doses of $5\text{x}10^{10}$ vp Ad26.COV2.S (release titer), using a NI margin of 2/3 for the GMC ratios (see Section 9.1).

The $2.5\text{x}10^{10}$ vp dose will be tested before the $7\text{x}10^{10}$ vp in the sequential testing due to an increased risk to fail non-inferiority as a consequence of a smaller sample size in the $7\text{x}10^{10}$ vp group.

4. STUDY DESIGN

4.1. Overall Design

Main Study

This is a randomized, double-blind Phase 3 study to evaluate 6 dose levels of Ad26.COV2.S administered as a 2-dose schedule in healthy adults. In this main study, the safety, reactogenicity,

and immunogenicity of Ad26.COV2.S of 1 dose (dose 1 of the 2-dose regimen) and 2-doses of Ad26.COV2.S will be evaluated (Table 1). The lower dose (3.5 $x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) levels mimic vaccine degradation to enable determination of product expiry. In order to increase the end of shelf-life specifications a potential target release titer of $7x10^{10}$ vp will be evaluated. A higher titer of $9x10^{10}$ vp will also be evaluated as is the upper limit of the release range (potential maximum vp at release). The study population will consist of healthy men and women aged between 18 and 55 years (inclusive), who have not previously received a vaccine against COVID-19 and have not had prior exposure to SARS-CoV-2 as assessed by local serology testing. Participants will receive Ad26.COV2.S administered IM.

A target of approximately, 1,350 participants in the main study (225 participants per active vaccine group [assuming approximately a 10.2% dropout]) will be randomized in parallel in a 1:1:1:1:1:1 ratio to 1 of 6 vaccination groups in this study. Participants will receive a 2-dose vaccination regimen at different dose levels (9×10^{10} vp, 7×10^{10} vp, 5×10^{10} vp, $3.5x10^{10}$ vp, $2.5x10^{10}$ vp,$1.25x10^{10}$ vp).

Table 1: Schematic Overview of Study Design and Groups for the Main Study

Group	N	Day 1 Vaccination 1	Day 57 Vaccination 2
1	For NI ~ 225	Ad26.COV2.S $9x10^{10}$ vp	Ad26.COV2.S $9x10^{10}$ vp
2	For NI ~ 225	Ad26.COV2.S $7x10^{10}$ vp	Ad26.COV2.S $7x10^{10}$ vp
3	For NI ~ 225	Ad26.COV2.S $5x10^{10}$ vp	Ad26.COV2.S $5x10^{10}$ vp
4	For NI ~ 225	Ad26.COV2.S $3.5x10^{10}$ vp	Ad26.COV2.S $3.5x10^{10}$ vp
5	For NI ~ 225	Ad26.COV2.S $2.5x10^{10}$ vp	Ad26.COV2.S $2.5x10^{10}$ vp
6	For NI ~ 225	Ad26.COV2.S $1.25x10^{10}$ vp	Ad26.COV2.S $1.25x10^{10}$ vp

Sub Study

An additional enrollment of adult participants 18 to 55 years, inclusive, will enroll into a sub study, into Groups 1, 3, 5 and 6 (Table 2) to further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events. Participants will receive Ad26.COV2.S administered IM.

A target of approximately 240 participants will be enrolled in the sub study and will receive a 2-dose vaccination regimen at either 9×10^{10} vp, 5×10^{10} vp, $2.5x10^{10}$ vp, or $1.25x10^{10}$ vp. This target may not be met due to the challenges of enrolling seronegative subjects into the study, so sub-study enrollment may stop at lower numbers.

Table 2: Schematic Overview of Study Design and Groups for the Sub Study

Group	N (Seronegative)*	N (Seropositive)	Day 1 Vaccination 1	Day 57 Vaccination 2
1	~ 40	~ 20	Ad26.COV2.S $9x10^{10}$ vp	Ad26.COV2.S $9x10^{10}$ vp
3	~ 40	~ 20	Ad26.COV2.S $5x10^{10}$ vp	Ad26.COV2.S $5x10^{10}$ vp
5	~ 40	~ 20	Ad26.COV2.S $2.5x10^{10}$ vp	Ad26.COV2.S $2.5x10^{10}$ vp
6	~ 40	~ 20	Ad26.COV2.S $1.25x10^{10}$ vp	Ad26.COV2.S $1.25x10^{10}$ vp

*Due to the challenges of enrolling seronegative subjects into the study, study enrollment may stop at lower numbers.

Table 3: Humoral Immunity Blood Sampling Schedule in Participants in All Groups of the Main and Sub Study

		Month 1	Month 2	Month 3	Month 6*	
Groups**	**Day 1**	**Day 29**	**Day 57**	**Day 71**		
1 6	●	●	●	●	●	

*post last vaccination
**Groups 1, 3, 5 and 6 in the sub study

Table 4: SARS-CoV-2 Non-S Serology Schedule in Participants in All Groups of the Main and Sub Study

		Month 1	Month 2	Month 3	Month 6*	
Groups**	**Day 1**	**Day 29**	**Day 57**	**Day 71**		
1 6		●		●		

*post last vaccination
** Groups 1, 3, 5 and 6 in the sub study

Table 5: Serum Sampling and PaxGene Schedule for Innate MoA in Participants in Groups 1, 3, 5 and 6 of the Sub Study

Groups	Day 1*	Day 2	Day 4	Day 8	Day 57*	Day 58	Day 60	Day 64
1, 3, 5 and 6	●	●	●	●	●	●	●	●

*pre vaccination
MoA=mechanism of Action

An IDMC has been commissioned for the Ad26.COV2.S program. Any significant safety information will be shared with the IDMC. Refer to Committees Structure in Section 10.3, for details.

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

Study Duration

The study duration from screening until the last follow-up visit will be at least 8 months per participant. The study will consist of a 28-day screening phase with vaccinations on Day 1 and Day 57, and a follow-up of at least 6 months after the last vaccination.

The vaccination phase consists of the administration of 1-dose of Ad26.COV2.S on Day 1 and 1-dose of Ad26.COV2.S on Day 57. A follow-up of at least 6 months after vaccination 2, is foreseen.

If a participant is unable to complete the study (post vaccination 1), but has not withdrawn consent, an early exit visit will be conducted, or the participant can continue with other study procedures. 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, AESIs, and SAEs. Other safety assessments include vital

signs measurements (heart rate, supine systolic and diastolic blood pressure, respiratory rate, and body temperature) and physical examinations at the time points indicated in Section 1.4.

After each vaccination, participants will remain under observation at the study site for at least 15 minutes for presence of any acute reactions and solicited events. Any solicited local or systemic AEs, unsolicited AEs, MAAEs, AESIs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period. In addition, participants will record solicited signs and symptoms in a diary for 7 days post vaccination.

The reporting periods of AEs, MAAEs, AESIs, and SAEs, and special reporting situations are detailed in Section 8.3. Reporting periods for concomitant therapy are outlined in Section 6.8. At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing)

- the participant can continue in the study for safety follow-up if they choose to:
    - This should be in accordance with local country and site level recommendations, including requirements for quarantine
    - They will not be permitted to receive further study vaccination administrations
    - The study staff will recommend the participant informs their medical care provider.
    - If there are no local country recommendations for COVID-19, the sponsor recommends the participant self-quarantines and does not come for a clinic visit until 2 consecutive negative PCR tests could be obtained.

In case the participant experiences signs or symptoms of COVID-19 after obtaining a positive SARS-CoV-2 test result, they should contact the study site at the time of symptom onset for recommendations on actions to follow for further care per local guidance.

See Section 8.3.1 on the reporting periods of this event.

A final safety follow-up visit is foreseen at least 6 months after the last vaccination for all participants.

From all participants, blood samples will be collected at selected timepoints indicated in Section 1.4, Schedule of Activities for humoral immunogenicity assessments, with an emphasis on neutralizing and binding antibody responses. Further details about the immunogenicity assessments are provided in Section 8.1.

An independent IDMC has been installed for the different studies throughout the COVID-19 vaccine program. Refer to Section 10.3.6 for details.

The planned 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 Level Selection

The rationale behind the selection of the dose level of the release titer ($5x10^{10}$ vp) is described in Section 4.3.

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

Rationale for the Sub Study

The mechanism for the rare thrombosis with thrombocytopenia syndrome (TTS) events that have been reported after vaccination with Johnson & Johnson's Ad26.COV2.S vaccine is not known. Examining gene expression in blood cells may inform on the inflammation signals and pro-thrombotic signaling pathways triggered by Ad26.COV2.S that can predispose for TTS. Gene expression profiles will be generated from blood obtained from clinical trials to provide insights into putative signaling pathways that may predispose for TTS and that are triggered by Ad26.COV2.S. Whole blood RNA will be sampled on early timepoints after vaccination with Ad26.COV2.S at different dose levels, examining if the innate gene expression patterns are dose dependent. In addition, serum samples collected at early timepoints can inform on systemic cytokines and chemokines and lipid mediators of innate activation to complement the transcriptome analysis. To further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events, an additional sub study consisting of a target of approximately 40 seronegative and 20 seropositive participants to Groups 1, 3, 5 and 6 has been added to the study. This sub study will obtain blood samples at additional timepoints for additional analyses of transcriptome and serum innate responses as outlined above to further explore the mechanism of these TTS events.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be

withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Potential participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is that this study will be performed in adult participants who will receive no benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study. See Section 2.3, Benefit-Risk Assessment for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based up the US Department of Health and Human Services Office for Human Research Protections, and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period (US FDA 1998, US DHHS 1998), and as well as the European Commission guidelines of 500 mL per donation and 3 L per consecutive 12 month period (EC 1998).

4.3. Justification for Dose

The release titer of Ad26.COV2.S in the present study (5×10^{10} vp) is based on experience with other Ad26-vectored vaccines administered to adults in clinical studies including Ad26.ZEBOV (Ebola virus program); Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV program); Ad26.CS.01 (malaria program); Ad26.RSV.FA2 and Ad26.RSV.preF (RSV program); and Ad26.ZIKV.001 (Zika virus program). The dose level of 5×10^{10} vp is the most extensively tested dose to date and has shown to be well tolerated and immunogenic in these vaccine programs. Safety data from studies with other Ad26-based vaccines are summarized in Section 2.2.

The same dose level is also being assessed in study VAC31518COV1001 where initial immunogenicity and safety data (28 days post-dose 1 data from Cohort 1a and available data from Cohort 3) have demonstrated that a single-dose of Ad26.COV2.S at 5×10^{10} vp and 1×10^{11} vp induces an immune response that meets prespecified minimum criteria and is safe. The sponsor has therefore decided to proceed with a 5×10^{10} vp as the release titer dose in this Phase 3 study. The additional dose levels of 9×10^{10} vp, 7×10^{10} vp, 3.5×10^{10} vp, 2.5×10^{10} vp and 1.25×10^{10} vp were chosen to be evaluated based on data from the COV2001 study. The lower dose ($3.5\ x10^{10}$ vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$ vp) levels mimic vaccine degradation to enable determination of product expiry. In order to increase the end of shelf-life specifications a potential target release titer of $7x10^{10}$ vp will be evaluated. A higher titer of $9x10^{10}$ vp will also be evaluated as is the upper limit of the release range (potential maximum vp at release). The present study incorporates a 2-dose regimen, as this dosing schedule is also being evaluated by the sponsor across clinical trials. While a 1-dose regimen demonstrated efficacy and safety for emergency use in a pandemic setting, the long-time efficacy and safety are still being evaluated. The duration of immunity of 2-doses may be preferable post-acute pandemic setting.

Non-human primates immunized with a single-dose of Ad26.COV2.S (Study 20-14, dose level titration study) showed robust protection after intranasal and intratracheal challenge with

SARS-CoV-2. Ad26.COV2.S at 5×10^{10} vp provided complete protection in the lung in 5 of 5 animals, and in 5 of 6 animals in the upper respiratory tract. All control animals showed substantial viral load in both the lower and upper respiratory tract.

4.4. End of Study Definition

End of Study Definition

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

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at the 6-month follow-up visit post-dose 2 vaccination for their respective study group.

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

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study vaccine. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

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

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccination is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study (See Section 5.4, Screen Failures, describes options for retesting). The required source documentation to support meeting the enrollment criteria is noted in Section 10.3.1.

5.1. Inclusion Criteria

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

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

2. Participant is willing and able to adhere to the prohibitions and restrictions specified in this protocol.
3. Participant is 18 to 55 years of age, inclusive, on the day of signing the ICF.
4. Criterion modified per Amendment 1:

4.1 Participant must have a BMI <35.0 kg/m^2.

5. Criterion modified per Amendment 1:

5.1 Participant must be healthy, in the investigator's clinical judgment, as confirmed by medical history, physical examination, and vital signs performed at screening. Participant may have underlying illnesses, as long as the symptoms and signs are medically controlled and not considered to be comorbidities related to an increased risk of severe COVID-19[a], except for smoking, which is allowed (see also exclusion criterion 21). If on medication for a condition, the medication dose must have been stable for at least 12 weeks preceding vaccination and expected to remain stable for the duration of the study. Participant will be included on the basis of physical examination, medical history, and vital signs[b].

6. Criterion modified per Amendment 1:

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

Before randomization, participants must be either (as defined in Section 10.5):

a. Not of childbearing potential

b. Of childbearing potential and practicing a highly effective method of contraception and agrees to remain on such a method of contraception from signing the consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the 1st administration of study vaccine. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the 1st vaccination. Highly effective methods for this study include:

1. hormonal contraception:

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

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

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

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

[c] Use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms (CDC 2021).

2. intrauterine device;
3. intrauterine hormone-releasing system;
4. bilateral tubal occlusion/ligation procedure;
5. vasectomized partner (the vasectomized partner should be the sole partner for that participant);
6. sexual abstinence*.

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

7. Criterion modified per Amendment 1:

   7.1 All female participants of childbearing potential must:

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

   b. Have a negative highly sensitive urine pregnancy test immediately on the day of and prior to each study vaccine administration.

8. Participant agrees to not donate bone marrow, blood, and blood products from the first study vaccine administration until 3 months after receiving the last dose of study vaccine.
9. Participant must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

5.2. Exclusion Criteria

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

1. Participant has a clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned first dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.
2. Participant has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
3. Participant has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine; refer to IB).
4. Criterion modified per Amendment 1

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

   a. Clinical conditions (eg, autoimmune disease, potential immune mediated disease or known or suspected immunodeficiency, chronic kidney disease [with dialysis]) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment eg, autoimmune

thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Non-immunomodulator treatment is allowed as well as steroids at a non-immunosuppressive dose or route of administration.

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

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

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

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

7. Criterion modified per Amendment 1

7.1 Participant received treatment with immunoglobulins in the 3 months or exogenous blood products (autologous blood transfusions are not exclusionary) in the 4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.

8. Participant received or plans to receive:

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

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

9. Criterion modified by Amendment 1

9.1 Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational Ig or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.

Note: Participation in an observational clinical study is allowed at the investigator's discretion; please notify the sponsor (or medical monitor) of this decision.

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

The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination (see also Exclusion Criterion 19) and during the study except under the conditions described in Section 6.6.

10. Participant is a woman who is pregnant or planning to become pregnant within 3 months after the last dose of study vaccine.
11. Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
12. Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after the last dose of study vaccine administration.
13. Participant has a contraindication to IM injections and blood draws eg, bleeding disorders.
14. Criterion reintroduced per Amendment 2.

    14.1 Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.
15. Participant has chronic active hepatitis B or hepatitis C infection per medical history.
16. Participant has had major psychiatric illness or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
17. Participant cannot communicate reliably with the investigator.
18. Participant who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study or is unlikely to complete the full course of vaccination and observation.
19. Participant previously received a coronavirus vaccine.
20. Criterion modified by Amendment 4

    20.1 Criterion modified by Amendment 6

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

    Note: For participants in the sub study, a positive diagnostic test for past SARS-CoV-2 testing (serological testing) does not exclude the participant from the study as a target of approximately 40 seronegative and 20 seropositive participants per group (Group 1, 3, 5 and 6) will be enrolled in the sub study. Seropositive participants are not excluded up to the point when 20 seropositive participants are recruited only.
21. Criterion modified by Amendment 1

    21.1 Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19, ie, participants with moderate-to-severe asthma; chronic lung diseases such as COPD (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital

heart disease, cardiomyopathies, and (pulmonary) hypertension or high blood pressure; obesity (BMI ≥ 35 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; and other immunodeficiencies; hepatitis B infection; and sleep apnea, and participants who live in nursing homes or long-term care facilities. This list is consistent with the list of conditions that increase the risk of progression to severe COVID-19 available at the CDC website at the time of writing of this protocol (CDC 2020c), except for smoking, which is allowed. The data from the CDC website is summarized in Section 10.7. Participants may have hypertension of mild severity, as long as it is stable and medically controlled as defined by no change in medication over the past 6 months (except for issues of tolerability or use of similar drug with same mechanism of action, eg, thiazides, Beta blockers, Alpha blockers at the same effective dose).

22. Participant who is currently working in an occupation with a high risk of exposure to SARSCoV-2 infection (eg, health care worker or emergency response personnel who work in close contact with SARSCoV-2 infected patients) or considered at the investigator's discretion to be at increased risk to acquire COVID-19 for any other reason.
23. Participant who has had a known exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within 2 weeks of screening.
24. History of confirmed SARS or MERS.
25. Criterion added per Amendment 3
    25.1 History of capillary leak syndrome
26. Criterion added per Amendment 6
    26.1 History of TTS or heparin-induced thrombocytopenia and thrombosis (HITT)

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. Participants who are rescreened will be assigned a new participant number, undergo the ICF process again, and then restart a new screening phase.

5.5. Criteria for Temporarily Delaying Administration of Study Vaccine

The following events constitute a temporary contraindication to study vaccination:

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

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for one of the subsequent vaccinations, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in Section 1.4.1, Schedule of Activities).

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

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1. Study Vaccines Administered

Ad26.COV2.S will be supplied at a concentration of $2x10^{11}$ vp/mL as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer of Ad26.COV2.S will be supplied as diluent containing 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.

Participants will be vaccinated on Day 1 and Day 57.

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

$9x10^{10}$ vp dose level (Group 1):

- 0.5 mL is withdrawn from vial 1 containing 0.75 mL $2x10^{11}$ vp/mL and added to vial 2 containing 0.75 mL of $2x10^{11}$ vp/mL. 0.15 mL is withdrawn from a vial containing 1.2 mL formulation buffer and is added to vial 2 containing 1.25 mL $2x10^{11}$ vp/mL. The solution is mixed and 0.5 mL is withdrawn from vial 2 (Ad26.COV2.S vial) for dosing $9x10^{10}$ vp.

$7x10^{10}$ vp dose level (Group 2):

- 0.3 mL is withdrawn from a vial containing 1.2 mL formulation buffer and added to a vial containing 0.75 mL $2x10^{11}$ vp/mL. The solution is mixed and 0.5 mL is withdrawn from the Ad26.COV2.S vial for dosing $7x10^{10}$ vp.

$5x10^{10}$ vp dose level (Group 3):

- 0.75 mL of formulation buffer is added to a vial containing 0.75 mL $2x10^{11}$ vp/mL, providing $1x10^{11}$ vp/mL in a vial with an extractable volume of more than 1 mL. Then 0.5 mL will be withdrawn from this vial for dosing $5x10^{10}$ vp.

$3.5x10^{10}$ vp dose level (Group 4):

- 0.5 mL is withdrawn from vial 1 (Ad26.COV2.S vial) containing 0.75 mL $2x10^{11}$ vp/mL and added to a vial containing 1.2 mL formulation buffer, leading to solution A. 0.15 mL is withdrawn from vial 2 (Ad26.COV2.S vial) containing 0.75 mL $2x10^{11}$ vp/mL and added to solution A, leading to solution B. Solution B is mixed and 0.5mL withdrawn from solution B for dosing $3.5x10^{10}$ vp.

$2.5x10^{10}$ vp dose level (Group 5):

- 0.4 mL is withdrawn from a vial containing 0.75 mL $2x10^{11}$ vp/mL and added to a vial containing 1.2 mL formulation buffer. The solution is mixed and 0.5mL is withdrawn from the formulation buffer vial for dosing $2.5x10^{10}$ vp.

$1.25x10^{10}$ vp dose level (Group 6):

- Withdrawal 0.9 mL from a vial containing 1.2 mL formulation buffer and add it to vial 2 containing 1.2 mL formulation buffer. Withdrawal 0.3 mL from a vial containing 0.75 mL $2x10^{11}$ vp/mL and add to vial 2 with formulation buffer. The solution is mixed, and 0.5 mL is withdrawn from the formulation buffer vial 2 for dosing $1.25x10^{10}$ vp.

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. In all circumstances, IM injections in other locations than the upper arm are not considered protocol deviations.

For information on vaccination windows, see Section 1.4.1 (for the sub study), Schedule of Activities. If a participant cannot be vaccinated within the allowed window (eg, if the window is missed due to a study pause [see Section 6.9 Study Pausing Rules]), 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 for a list of excipients (IB Ad26.COV2.S. 2022).

Refer to the study site investigational product and procedures manual (SIPPM) 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 SIPPM for additional guidance on study vaccine preparation, handling, and storage.

An unblinded study site pharmacist, or other qualified individual, who will have no other study function, will prepare the appropriate vials and syringes, labeled with the participant's identification number, and provide the syringes for the study vaccine in a blinded manner to the blinded vaccine administrator (a trained and qualified study nurse, medical doctor, otherwise qualified health care professional [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 study site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the vaccine accountability form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine accountability form.

Potentially hazardous materials containing hazardous liquids, such as needles and syringes, should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to participants participating in the study. Returned study vaccine must not be dispensed again, even to the same participant. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study vaccine are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Vaccine Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 6 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. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

If, due to the urgency of study initiation during the ongoing pandemic, the IWRS is not yet available at the planned time of randomization of the first participant, randomization may be started based on a paper randomization list until the IWRS is live. In the event that randomization is started based on a paper randomization list, sealed randomization codes will be provided for each participant containing coded details of study vaccine allocation. All randomization codes, whether opened or sealed, will be collected after the end of the participant's participation in the study.

Blinding

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

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

Data that may potentially unblind the study vaccine assignment (ie, immunogenicity data, study vaccine accountability data, study vaccine allocation, biomarker, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the

potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, or others as appropriate until the time of database lock and unblinding.

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

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

In general, randomization codes will be disclosed fully only if the study is completed, and the clinical database is closed.

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 at the efficacious dose if/when these become available, including the sponsors. In these cases, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see Section 6.8).

If the participant prefers another company's vaccine, they will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event of the participant unblinding in order to receive an authorized/licensed COVID-19 vaccine, no further study vaccination will be permitted. Unblinded participants will be asked to continue to be followed in this study in line with the Schedule of Activities (SoA) to the extent that they permit. Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding, for safety and immunogenicity analysis, as described in the Statistical Analysis Plan (SAP).

6.4. Study Vaccination Compliance

Study vaccines will be administered intramuscularly by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the eCRF (including date and time of injection [deltoid or alternative location]). For blinding procedures, see Section 6.3, Measures to Minimize Bias: Randomization and Blinding.

6.5. Dose Modification

Dose modification is not applicable in this study.

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

For all participants, given that approved COVID-19 vaccines exist for the adult population in all countries in which VAC31518COV3003 is being conducted, if participants need to receive 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. Once primary analysis results are available (post vaccination 2), investigators will be notified to contact participants in groups who received a dose level of Ad26.COV2.S that did not meet non-inferiority post vaccination 2 to advise them that they should receive a booster of a COVID-19 vaccine that is licensed/authorized through their national COVID-19 vaccination health care program if not already received.

At the time when a COVID-19 vaccine is determined to be efficacious and authorized/licensed for use, some participants may become eligible to receive such vaccine at the efficacious dose, depending on country-specific conditions (eg registration status, local recommendations/regulations, vaccine availability or the specific target group for vaccination). The investigator will discuss with the participants the available information and options to allow the participant to make an informed choice as to whether they qualify to receive the authorized/licensed vaccine and whether they should request individual unblinding to take up the offer of an authorized/licensed COVID-19 vaccine. In the event of the participant unblinding in order to receive an authorized/licensed COVID-19 vaccine, no further study vaccination will be permitted. Safety evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding for safety, efficacy and immunogenicity (under the conditions outlined in Section 6.3), as described in the SAP.

6.7. Treatment of Overdose

For this study, any dose of Ad26.COV2.S greater than the highest dose tested in the study will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/MAAEs/AESIs/SAEs (ie, the participant will remain at the study site for at least 15 minutes and will be closely monitored for allergic or other

reaction by study staff. Follow-up telephone calls 12 hours and 24 hours post-dose will be made).

- Document the quantity of the excess dose in the eCRF.
- Report as a special reporting situation.

6.8. Prestudy and Concomitant Therapy

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

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

For all participants, concomitant therapies associated with an SAE, or suspected AESI meeting the criteria outlined in Section 10.4.1 and Section 8.3.6, respectively, will be collected and recorded in the eCRF from the moment of vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of vaccination until 6 months after vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study.

For all participants, concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of vaccination through 28 days after vaccination. Concomitant therapies associated with solicited AEs will be collected by the participants and recorded in the eCRF from the time of vaccination through 7 days after vaccination.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed. Any participant who has been given an anti-COVID-19 vaccine (other than study vaccine) or treatment will not receive further study vaccination. Participants may not receive an investigational drug (including investigational drugs for prophylaxis of COVID-19) or use an invasive investigational medical device within 30 days or receive an investigational Ig or monoclonal antibodies within 3 months, or receive convalescent serum for COVID-19 treatment within 4 months or receive an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the first dose of study vaccine.

Licensed live attenuated vaccines should be given at least 28 days before or at least 28 days after a study vaccination. Other licensed (not live) vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before or at least 14 days after administration of study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. The use

of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S is disallowed at any time prior to vaccination and during the study. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Antipyretics are recommended post vaccination for symptom relief as needed. Prophylactic antipyretic use is not encouraged; however, in some instances, it could be considered for participants with special circumstances and/or comorbidities.

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

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

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.9. Study Vaccination Pausing Rules

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 study visits out of window during a study pause are not considered to be protocol violations, however, the data at these timepoints may be eliminated from some statistical analyses.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants must not receive any further doses of study vaccine but should remain on study for follow-up with assessments of safety and immunogenicity as indicated in Section 1.4.1 and Section 1.4.2 (for the sub study), Schedule of Activities. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data

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

- Unblinding of a study participant in order to receive an authorized/licensed COVID-19 vaccine
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of systemic corticosteroids at immunosuppressive dose, and administration of antineoplastic and immunomodulating agents or radiotherapy
- Withdrawal of consent to receive further study vaccination
- Participant has a positive test result for SARS-CoV-2 infection during the study after screening and enrollment (see Section 8.3.1).
- 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, including CVST or HITT or GBS.
- Participant experiences capillary leak syndrome after the first dose.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent from the study
- Death
- Repeated failure to comply with protocol requirements

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

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 10.3.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.4) summarizes the frequency and timing of safety, reactogenicity, immunogenicity, and other measurements applicable to this study. All participants in the study will be counselled on COVID-19 prevention each time that they have a contact with study site staff in line with local guidelines.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: vital signs before blood draws. If needed, assessments may be performed at another day within the applicable visit window. Actual dates and times of assessments will be recorded in the source document and in the eCRF.

Participants will be provided a thermometer (to measure body temperature), ruler (to measure local injection site reactions), and participant diary to record body temperature and solicited local (at injection site) and systemic signs and symptoms. The diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms post vaccination (reactogenicity). The study staff is responsible for providing appropriate training to the participant

to avoid missing or incorrect data. The diary will be reviewed by the study personnel at visits indicated in Section 1.4, Schedule of Activities. If the diary review is missed, the diary will be reviewed during the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be completed.

The total blood volume to be collected from each participant over the course of the main study will be approximately 119 mL. The total blood volume to be collected from each participant over the course of the sub study will be approximately 163 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. For participants who experience a suspected AESI, an additional 30 mL of blood will be collected.

At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing), the participant should contact the study site at the time the positive SARS-CoV-2 test result is obtained. The participant can continue in the study for safety follow-up if they choose to; however, this must be in accordance with local country and site level recommendations for COVID-19, including requirements for quarantine. These participants will not be permitted to receive further study vaccination administrations. The study staff will recommend the participant informs their medical care provider. If there are no local country recommendations for COVID-19, the sponsor recommends the participant self-quarantines and does not come for a clinic visit until 2 consecutive negative PCR tests could be obtained. If the participant experiences signs or symptoms of COVID-19 after obtaining a positive SARS-CoV-2 test result, they should contact the study site at the time of symptom onset for recommendations on actions to follow for further care. See section 8.3.1 on the reporting periods of this event.

Visit Windows

Visit windows are provided in Section 1.4, Schedules of Activities. The participant should be encouraged to come on the exact day planned and use the visit window only if absolutely necessary.

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

If a vaccination window is missed due to a study pause (see Section 6.9), efforts will be made to still vaccinate the participant as soon as possible, even if out of window. The timings of the post vaccination visits will be determined relative to the actual day of the vaccination, unless they overlap with other scheduled visits, in which case the sponsor should be contacted to discuss optimal scheduling for these visits. If the participant does not want to receive the second vaccination, they can still continue with other study procedures.

Screening

Screening will be performed within 28 days prior to the first study vaccination or on the day of vaccination. If screening is performed on the day of vaccination, Visit 1 and Visit 2 will coincide

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

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study-specific screening consent process, but only if the relevant pre-screening tests are identical to the per protocol screening tests and are within 4 weeks prior to first vaccination. However, no study-specific procedures, other than these pre-approved pre-screening assessments, will be performed until the participant has signed the study-specific ICF. Participants who test positive will be informed of the result by the study staff. The study-specific ICF date will be entered into the eCRF. The non-study-specific ICF will be considered source data.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to Section 1.4, Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for Ad26.COV2.S
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- Pharmacy manual/SIPPM/IPPI
- Laboratory manual and laboratory supplies
- eCOA Manual
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Participant Diaries
- Contact information pages

8.1. 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

substitute non-inferiority testing to immune responses to vaccine at release, as outlined in a revised analytical plan.

Venous blood samples will be collected for assessment of humoral immune responses in all participants. Sample volumes and time points are detailed in the Schedule of Activities in Section 1.4.

If the participant is unable to complete the study without withdrawing consent, immunogenicity samples will be taken at the early exit visit, but only if the early exit visit is at least 10 days after the previous immunology blood draw. See Section 1.4, Schedule of Activities for further details.

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

Table 6: Summary of Humoral Immunogenicity Assays[a]

Assay	Purpose
Humoral Immunogenicity	
Primary/Secondary/Exploratory endpoints	
SARS-CoV-2 binding antibodies (ELISA)	Analysis of antibodies binding to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein)
Exploratory endpoints	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type virus and/or pseudovirion expressing S protein, including emerging SARS-CoV-2 variants.
SARS-CoV-2 binding antibodies (ELISA or equivalent assay)	Analysis of binding antibodies to SARS-CoV-2 proteins (eg, S-protein), including emerging SARS-CoV-2 variant proteins.
SARS-CoV-2 binding antibodies (non-S ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to the SARS-CoV-2 N protein
Adenovirus neutralization	Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector
Functional and molecular antibody characterization	Analysis of antibody characteristics including Fc-mediated viral clearance, avidity, Fc characteristics, Ig subclass and IgG isotype
Epitope-specificity characterization	Analysis of site-specificity, epitope mapping
Cytokine profiling, and analysis of circulating Spike protein	Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma, and analysis of circulating Spike protein.
Passive transfer	Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model
Innate Assessments (*Exploratory endpoints)*	
Gene expression analysis	Analysis of gene expression by RNA transcript profiling in whole blood (ex vivo, PaxGene tubes)
Proteomic and/or lipidomic approaches, and analysis of circulating Spike protein	Analysis of protein translates (including circulating Spike protein) or lipid mediators in serum or plasma.

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

[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 serological testing outside the study.

8.2. Safety Assessments

Details regarding the IDMC are provided in Section 10.3.6.

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

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

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

The study will include the following evaluations of safety and reactogenicity according to the time points provided in the Schedule of Activities (Section 1.4).

8.2.1. Physical Examinations

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

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

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

8.2.2. Vital Signs

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

Participants will utilize a diary to record body temperature measurements post vaccination (see Section 8).

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

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

8.2.3. Pregnancy Testing

A urine pregnancy test for participants of childbearing potential will be performed at screening and before each vaccination.

Additional pregnancy tests may be performed for participants of childbearing potential, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.2.4. Clinical Laboratory Assessments

Blood samples for clinical laboratory assessments will be collected as described in the Schedules of Activities in Section 1.4 and Section 10.2, Appendix 2. 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 10.8, Appendix 8) 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 1.4 and Section 10.2, Appendix 2). The Investigator will review the laboratory test results to assist the investigation of the AESI.

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

8.3. Adverse Events, Serious Adverse Events, 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, suspected AESIs, and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant for the duration of the study. Further details on AEs, SAEs, MAAEs, suspected 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

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

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

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

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

At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing; for participants seropositive at baseline, only PCR testing applies) 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. If the event occurs after 28 days, and it is not serious, it will be reported in the eCRF. The participant can continue in the study for safety follow-up if they choose to; however, this must be in accordance with local country and site level recommendations for COVID-19 and they will not be permitted to receive further study vaccination administrations. Any positive SARS-CoV-2 result should be recorded in the eCRF.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) will 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 room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic diseases will be collected as part of the MAAEs. MAAEs are to be reported for all participants from the moment of vaccination until 6 months after the vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.

Adverse Events of Special Interest

Thrombosis with Thrombocytopenia Syndrome is considered to be an AESI. Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/µL [Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome (TTS) 2021]) will be recorded from the moment of vaccination until the end of the study/early withdrawal (see Section 8.3.6). An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS.

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

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

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

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

8.3.2. Method of Detecting Adverse Events, Medically-attended Adverse Events, 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.

Solicited Adverse Events

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at injection site) and systemic events for which the participant is specifically questioned, and which are noted by participants in their diary.

After each vaccination, participants will remain under observation at the study site for at least 15 minutes for the presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in a diary for 7 days post vaccination. All participants will be provided with a diary and instructions on how to complete the diary (see Overview in Section 8, Study Assessments and Procedures). Electronic diary information will be transferred from the Safety Diary source to the sponsor. After review and verbal discussion of the initial electronic diary entries with the participant, the investigator will complete his/her own assessment in the relevant sections of the eCRF. Once a solicited sign or symptom from a diary is considered to be of severity Grade 1 or above, it will be recorded as a solicited adverse event.

Solicited Injection Site (Local) Adverse Events

Participants will be asked to note in the diary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 7 days post vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in the references (Gidudu 2012, Kohl 2007).

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. If more than 1 measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least 1 measurement (Marcy 2004).

Participants will also be instructed on how to note signs and symptoms in the diary on a daily basis for 7 days post vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, and myalgia.

Unsolicited Adverse Events

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

Medically-attended Adverse Events

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

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

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

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities

unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in 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 but will remain in the study and will continue to undergo all procedures for follow-up and all safety follow-up as outlined in the protocol for all participants.

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

8.3.6. Adverse Events of Special Interest

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

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

Specific requirements for the AESI are described below.

8.3.6.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 2.3.1, Risks Related to Study Participation, TTS has been observed very rarely following vaccination with Ad26.COV2.S and is considered to be an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia (American Society of Hematology 2021, Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome 2021).

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 10.8, Appendix 8. A suspected TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.9, Appendix 9

- Thrombocytopenia, defined as platelet count below 150,000/μL (Brighton Collaboration. Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome 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 may 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 1.4.3). 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 10.8, Appendix 8 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.

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

Formal NI testing will be applied to demonstrate NI of 1-dose and 2-doses of $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, and $1.25x10^{10}$ vp Ad26.COV2.S versus 1- dose and 2-doses of $5x10^{10}$ vp Ad26.COV2.S (release titer), using a NI margin of 2/3 for the GMC ratios.

The $2.5x10^{10}$ vp dose will be tested before the $7x10^{10}$ vp in the sequential testing due to an increased risk to fail non-inferiority as a consequence of a smaller sample size in the $7x10^{10}$ vp group as shown in Table 7.

The following 2 sets of hypotheses (1 dose and 2 doses) will independently be tested sequentially:

Post-dose 1

1a) NI after 1-dose of Ad26.COV2.S $9x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

1b) NI after 1-dose of Ad26.COV2.S $2.5x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

1c) NI after 1-dose of Ad26.COV2.S $7x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

1d) NI after 1-dose of Ad26.COV2.S $3.5x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

1e) NI after 1-dose of Ad26.COV2.S $1.25x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

In this set, NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 28 days post-dose 1, using a NI margin of 2/3 for the GMC ratio (GMC [$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp]/GMC $5x10^{10}$ vp).

Post-dose 2

2a1) NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2a2) NI after 2-doses of Ad26.COV2.S $9x10^{10}$ vp versus 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2b1) NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2b2) NI after 2-doses of Ad26.COV2.S $2.5x10^{10}$ vp versus 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2c1) NI after 2-doses of Ad26.COV2.S $7x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2c2) NI after 2-doses of Ad26.COV2.S $7x10^{10}$ vp versus 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2d1) NI after 2-doses of Ad26.COV2.S $3.5x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2d2) NI after 2-doses of Ad26.COV2.S $3.5x10^{10}$ vp versus 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer)

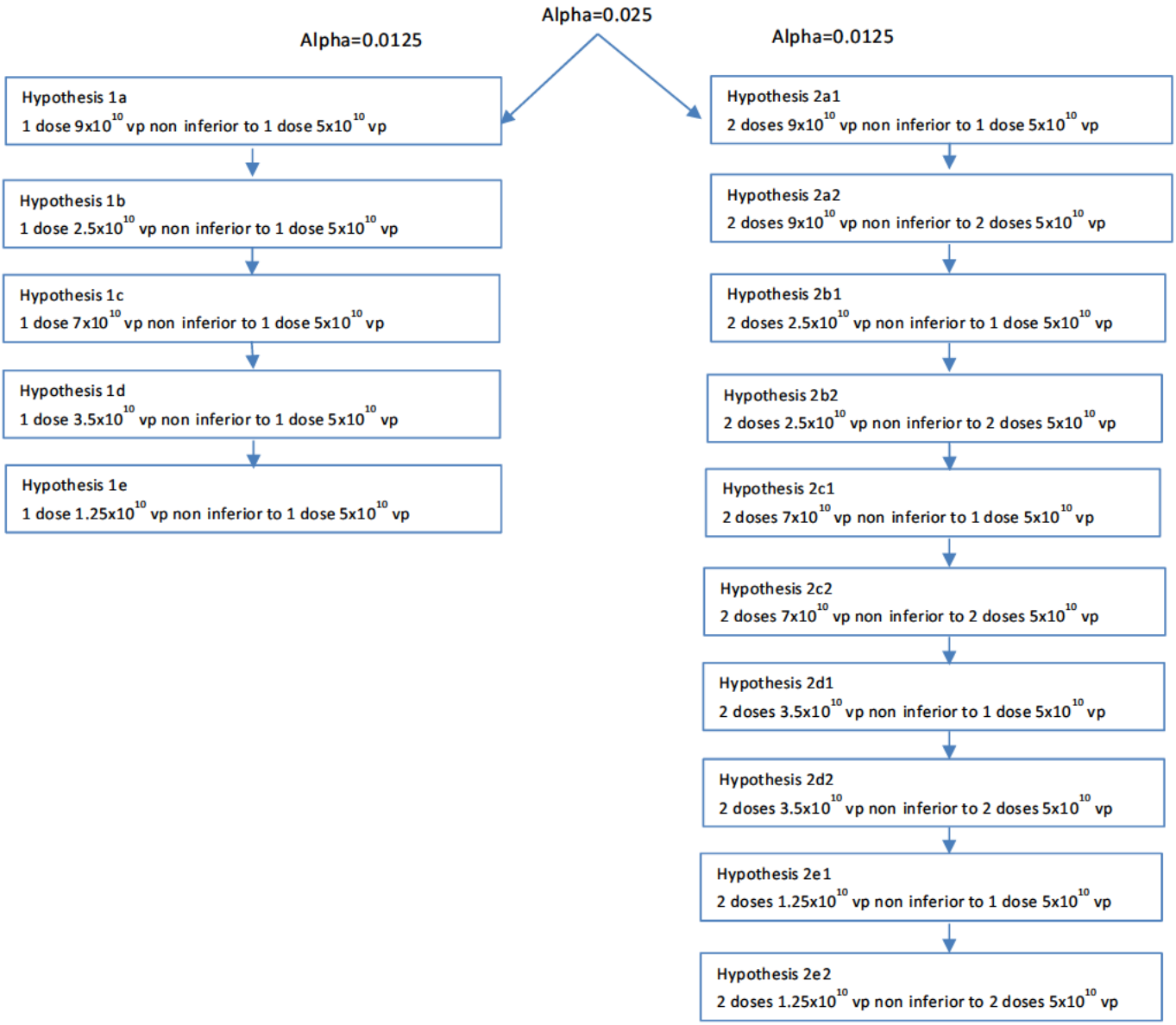
2e1) NI after 2-doses of Ad26.COV2.S $1.25x10^{10}$ vp versus 1-dose of Ad26.COV2.S $5x10^{10}$ vp (release titer)

2e2) NI after 2-doses of Ad26.COV2.S $1.25x10^{10}$ vp versus 2-doses of Ad26.COV2.S $5x10^{10}$ vp (release titer)

In this set, NI will be demonstrated in terms of humoral immune response expressed by the GMCs of S-ELISA, 14 days post-dose 2 ($9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp) and 28 days post-dose 1 or 14 days post-dose 2 ($5x10^{10}$ vp), using a NI margin of 2/3 for the GMC ratio (GMC $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp]/GMC $5x10^{10}$ vp).

Figure 2 depicts a tree-based schema for testing the 2 sets of non-inferiority hypotheses (1 dose and 2 doses) controlling the family-wise error rate at alpha 0.025 (1-sided).

Figure 2: Decision Tree-Based Hypothesis Testing



9.2. Sample Size Determination

The number of participants chosen is to provide sufficient power for the non-inferiority comparisons stated in Section 9.1.

The following assumptions were made in the sample size determinations:

- Log transformed (log10 scale) immune response data are normally distributed
- A common standard deviation (SD): SD 0.5 (log10 scale) of the immune response log transformed data
- Non-inferiority margin log10(2/3) -0.176

- Alpha 0.025 (one-sided). Using a Bonferroni correction, Type I error will be split equally over the 1-dose and 2-dose comparisons: 0.0125 (1-sided) for 1- and 2-dose NI comparisons
- Power 90%

Based on the above assumptions, assuming approximately a 10.2% dropout, a sample size of 225 participants per active vaccine group (see Table 1) is needed to detect non-inferiority of testing 1-dose and 2-doses of $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, and $1.25x10^{10}$ vp Ad26.COV2.S as the test groups versus 1-dose and 2-doses of $5x10^{10}$ vp Ad26.COV2.S (release titer) as the reference groups, with 90% power.

A target of approximately 240 participants (40 seronegative and 20 seropositive participants) per dose regimen in Groups 1, 3, 5, and 6 will be enrolled to further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to Ad26.COV2.S to better understand a possible risk to TTS events. This target may not be met due to the challenges of enrolling seronegative subjects into the study, so sub-study enrollment may stop at lower numbers.

Participants in the main study and sub-study (participants who are seronegative at enrollment or baseline) may be combined for the analysis.

Table 7 shows how the power will be affected with 10%, 20%, 30%, 40%, 50% and 60% dropout due to various reasons (eg, lost to follow-up, participants with major protocol deviations with impact on immunogenicity, participants who become N-seropositive during the study or with a confirmed SARS-CoV-2 infection, and participants who received their vaccination outside the allowed window).

Table 7: Power Based on % of Drop Out

			% drop out since enrollment					
Regimen	**sample size at enrollment per arm**	**group**	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**
$9x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	1	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$2.5x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	5	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$7x10^{10}$ vp (main study)	212	2	89.40%	85%	79.90%	72.70%	63.70%	53.00%
$5x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	3	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%
$3.5x10^{10}$ vp (main study)	212	4	89.40%	85.00%	79.90%	72.70%	63.70%	53.00%
$1.25x10^{10}$ vp (sample size of main study and sub-study)	252 (212+40)	6	92.00%	88.60%	83.70%	76.80%	68.10%	57.20%

9.2.1. Immunogenicity

The primary objective of this study is to demonstrate the NI, in terms of humoral immune response, of a 1-dose and 2-doses of $9x10^{10}$ vp, $2.5x10^{10}$ vp, $7x10^{10}$ vp, $3.5x10^{10}$ vp, and $1.25x10^{10}$ vp Ad26.COV2.S versus a 1-dose and 2-doses of $5x10^{10}$ vp Ad26.COV2.S (release titer).

The S-ELISA has been selected as primary endpoint since samples from all participants will be analyzed using this assay, which has an improved throughput as compared to VNA. The ELISA will be used as primary endpoint for NI comparison, provided that a robust correlation can be confirmed between ELISA and VNA. Otherwise, VNA may be considered for the primary endpoint. In this case, to accelerate availability of results, only samples collected 28 days post-dose 1 or 14 days post-dose 2 will be tested with VNA but not baseline samples.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

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

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

NI: The NI analysis set will include all PPI participants who are SARS-COV-2 seronegative at study entry.

9.4. Statistical Analyses

The SAP will be finalized prior to the first data base lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. One Statistical Analysis Plan (SAP) will be provided for both the main study and the sub study.

9.4.1. General Considerations

Analysis populations are defined in Section 9.3. Planned analyses are defined in Section 9.5.

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

If a participant has a positive SARS-CoV-2 test after vaccination, this participant will remain in the study, but samples obtained after SARS-CoV-2 infection will not be included in the per protocol immunogenicity analysis set.

9.4.2. Primary Endpoint(s)

Immunogenicity Endpoints

For each NI comparison between post-dose 1 ([$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp] versus $5x10^{10}$ vp), estimated humoral immune response differences will be expressed as ratios of GMCs of S-ELISA (GMC [$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp]/GMC $5x10^{10}$ vp), 28 days post-dose 1 with corresponding 97.5% confidence interval (CI) (2-sided) (Type 1 error 0.0125 for each comparison).

Similarly, for each NI comparison between post-dose 2 ([$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp] versus 1- or 2-doses of $5x10^{10}$ vp), estimated humoral immune response differences will be expressed as ratios of GMCs of S-ELISA (GMC [$9x10^{10}$ vp, $2.5x10^{10}$, $7x10^{10}$ vp, $3.5x10^{10}$ vp, or $1.25x10^{10}$ vp]/GMC $5x10^{10}$ vp), 28 days post-dose 1 or 14 days post-dose 2 with corresponding 97.5% confidence interval (CI) (2-sided) (Type 1 error 0.0125 for each comparison).

In both sets (1 dose and 2 doses) of comparisons above, 97.5% CIs (2-sided) for mean difference in log10-transformed S-ELISA titers between 2 groups will first be calculated and then back-transformed to the original scale to obtain the GMC ratios and the associated 97.5% CIs (2-sided). Non-inferiority between the groups will be established if the 97.5% CI of the estimated GMC ratio of the groups entirely lies above 2/3.

In the 1-dose (dose 1 of the 2-dose regimen) and 2-dose set NI comparisons, hierarchical testing after administration of a single-dose and 2 doses will be applied independently, as reflected in the Decision Tree-based Hypothesis Testing (Figure 2 and Section 9.1). The non-inferiority analyses will be done on the NI analysis set.

- Note: If a large number of participants become infected during the study (as assessed eg, by N-seroconversion or by PCR confirmation) or are SARS-CoV-2 seropositive at baseline, the main study and sub-study participants (seronegative at baseline) may be combined.
- If the power of the combined main study and sub-study is less than 80% then seropostive subjects at baseline will be included in the analysis. Further details of the analysis will be provided in the SAP.

9.4.3. Secondary Endpoint(s)

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 as applicable (GMC [S-ELISA]). Graphical representations of immunologic parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters, as applicable.

In addition, the ratio between neutralizing and binding antibodies as determined by S-ELISA and VNA, respectively, will be calculated together with confidence intervals. More details will be provided in the SAP.

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

Safety Endpoints

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

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the active vaccination phase (ie, AEs occurring after vaccination up to 28 days post vaccination), and all SAEs/MAAEs/AESIs will be included in the analysis. (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by vaccine group.

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

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

Clinical Laboratory Tests

Laboratory data (abnormal or graded, when available) will be listed and/or tabulated by participant and time point.

Vital Signs

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

Physical Examinations

Physical examination findings will be summarized at baseline. Physical examination abnormal findings will be listed.

9.4.4. Exploratory Endpoint(s)

The correlation between the binding antibody (ELISA) titers and neutralizing antibody (VNA) titers to SARS-CoV-2 will be assessed in a subset of participants at selected timepoints using Spearman's rank correlation, for example. Seronegative and seropositive participants in the sub study will be analyzed as a subgroup and shown in graphs using different colors and symbols. Additional details, including statistical methodology for analysis of other exploratory endpoints, will be provided in the SAP for both the main study and sub study.

9.4.5. Other Analyses

An IDMC has been commissioned for the Ad26.COV2.S program. Any relevant safety information from this study will be shared with the IDMC.

9.5. Planned Analyses

The sponsor may be unblinded for this study, but the blind will be maintained at the participant and study site level up to study end.

The primary analysis, which will be performed on unblinded data, will include safety up to Day 85 and immunogenicity up to Day 71 in the main study and sub study for all groups and will be performed when all participants have completed the visit that takes place 85 days after the first study vaccination or discontinued earlier.

The final analysis for the main study will be performed when all included participants from the main study have completed their last visit (at least 6 months post last vaccination) or discontinued earlier. Results from participants in the sub study may be available with the main study. Results from the main study and the sub study may be combined in one report.

Depending on availability of results, primary and final analysis might be combined.

Further 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 IDMC set for the program will have overview on the safety of this study.

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

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

unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded (see body of the protocol for more details).

If the participant prefers another company's vaccine, they will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. In the event of the participant unblinding in order to receive an authorized/licensed COVID-19 vaccine, no further study vaccination will be permitted. Unblinded participants will be asked to continue to be followed in this study in line with the Schedule of Activities (SoA) to the extent that they permit. Safety and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, if applicable and feasible. All data will be analyzed separately from the point of unblinding, for safety and immunogenicity analysis, as described in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

Ad26	adenovirus type 26
ADCC	antibody-dependent cell-mediated cytotoxicity
AdVAC®	adenoviral vaccine (vector platform)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	antigen presentation
AST	aspartate aminotransferase
BMI	body mass index
BUN	Blood Urea Nitrogen
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CPK	creatine phosphokinase
CVST	cerebral venous sinus thrombosis
eCRF	Electronic case report form(s)
CT	computed tomographic
DBL	data base lock
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
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
FIH	first-in-human
FOIA	Freedom of Information Act
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GLP	good laboratory practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
HIT	heparin-induced thrombocytopenia
HITT	heparin-induced thrombotic thrombocytopenia
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICS	intracellular cytokine staining
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL	interleukin
IM	intramuscular
IND	Investigational New Drug

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

Definitions of Terms

COVID-19	COVID-19 is the disease caused by the virus SARS-CoV-2. COVID-19 refers to SARS-CoV-2 infection with symptoms, and can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death (US FDA 2020a, US FDA 2020b).
eCOA	An umbrella term encompassing different types of outcomes assessments, in particular, the Safety Diary.
Safety Diary	The electronic technology used to record solicited signs and symptoms by the participants in the Safety Subset.

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities (Section 1.4.1 and Section 1.4.2:

Laboratory Assessments	Parameters	Timepoints
Testing done locally/centrally	• Urine pregnancy testing for participants of childbearing potential only	• At screening and before each vaccination
	• Nasal swab sample and test for SARS-CoV-2 antibody	• At screening and pre-vac 1 if the screening test was done more than 4 days before Day 1
	• Serology test for anti-SARS-CoV-2 N antibody	• At screening, At 28 days post-vac 1 and 14 days post-vac 2, and 24 weeks post-vac 2-. Testing may also be performed at 24 weeks post vac 2 from the humoral immunogenicity sample.
	• Whole blood sample for platelet count which at some sites may be part of a complete blood count with differential	• Pre-vac 1, 28 days post-vac 1, pre-vac 2, and 14 days post-vac 2 with Ad26.COV2.S and as part of a (suspected) AESI investigation if applicable
	• Serum samples for humoral immunogenicity	• Pre-vac 1, 28 days post-vac 1, pre-vac 2, 14 days post-vac 2 and 24 weeks post-vac 2 2
	• Serum/plasma samples for coagulation-related assays such as but not limited to: o Activated partial thromboplastin time o Prothrombin time o International normalized ratio o Fibrinogen o D-dimer· o Lupus anticoagulant· o Anti-cardiolipin antibody o Beta-2 glycoprotein· o Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay) o Platelet activation assay (if HIT/PF4 is positive) o Homocysteine· o ADAMTS13 Activity and Inhibitor Profile	• Based on the clinical evaluation of the suspected AESI (eg, whether thrombocytopenia is observed with a thrombotic event), all or some of these tests may be conducted on the stored pre-vaccination sample (some of these tests will be conducted retrospectively) and on the samples obtained as part of the AESI investigation • For all subjects from the main and sub study, at Pre-vac 1, 28 days post-vac 1, pre-vac 2, 14 days post-vac 2, all or some of these tests may be conducted on the samples (some of these tests will be conducted retrospectively)

Laboratory Assessments	Parameters	Timepoints
	• Analysis of messenger ribonucleic acid (mRNA) expression levels of vaccine-induced innate responses	• Pre-vac 1, 1 day post-vac 1, 3 days post-vac 1, 7 days post-vac 1, pre-vac 2, 1 day post-vac 2, 3 days post-vac 2 and 7 days post-vac 2
	• Analysis of cytokines, chemokines, and other protein- or lipid mediators of the innate immune response	• Pre-vac 1, 1 day post-vac 1, 3 days post-vac 1, 7 days post-vac 1, 1 day post-vac 2, 3 days post-vac 2 and 7 days post-vac 2

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants

- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

Country Selection

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

Other Ethical Considerations

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

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw

consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

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

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

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand vaccination with Ad26 based vaccines including Ad26.COV2.S, to understand SARS-CoV-2 infection, to understand differential vaccine responders, and to develop tests/assays related to Ad26-based vaccines and to Ad26.COV2.S and SARS-CoV-2 infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

10.3.6. Safety Monitoring Committees Structure

Independent Data Monitoring Committee

An IDMC has been established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

The IDMC will review data as indicated in Section 4.1.

Ad hoc review may be performed further to the occurrence of any AE/SAE, or at request of the sponsor's medical monitor or designee. The principal investigator and sponsor's study responsible physician will inform the IDMC of any AE of concern.

AESI Adjudication Committee

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding Ad26.COV2.S or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator

agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.COV2.S, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory 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 or eCOA. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into 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 (including medical history and prestudy medication), and study identification; study discussion and date of signed informed consent; dates of visits; results of safety parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

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

Participant- and investigator-completed scales and assessments designated by the sponsor (ie, diary to record solicited AEs, daily signs) will be recorded and will be considered source data. The participant's diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

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

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

10.3.11. Monitoring

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

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

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

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

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

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, Medically-attended Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH).

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

Any respiratory tract infection that is not due to SARS-CoV-2 infection will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. Any respiratory tract infection recorded as an AE in the eCRF will be excluded from any AE analysis if the molecular test is subsequently found to be positive for SARS-CoV-2. Respiratory tract infections arising from SARS-CoV-2 infection will not be reported as (S)AEs in the Clinical Study Report but will be tabulated separately. In general, any (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. In general, (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately.

Note: For time period of sponsor's AE collection, see All Adverse Events under Section 8.3.1.

Serious Adverse Event

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

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

- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a SUSAR even if it is a component of the study endpoint (eg, all-cause mortality).

At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test (whether through PCR or serological testing) 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 for safety follow-up if they choose to; however, this must be in accordance with local country and site level recommendations for COVID-19, and they will not be permitted to receive further study vaccination administrations. Any positive SARS-CoV-2 result should be recorded in the eCRF.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study vaccine is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study vaccine administration and the AE.

Not Related

There is not a reasonable causal relationship between study vaccine administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.

10.4.3. Severity Criteria

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007, included in Section 10.6.

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

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

The severity of solicited signs and symptoms will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified by the investigator using the toxicity grading scale in Section 10.6. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]).

10.4.4. Special Reporting Situations

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

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

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible,

diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

Serious Adverse Events

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

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

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

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

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

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

Adverse Events of Special Interest

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

10.4.6. Product Quality Complaint Handling

Definition

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

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

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

Definition of a Person of Childbearing Potential

A Person of Childbearing Potential

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

A Person Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is 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 total hysterectomy, bilateral tubal ligation/clip, and bilateral oophorectomy.

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

10.6. Appendix 6: Toxicity Grading Scale

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

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain/Tenderness[#]	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever	Hospitalization; Pain/tenderness causing inability to perform basic self-care function
Erythema[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis or exfoliative dermatitis
Swelling[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis

[#] Revised by the sponsor.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	> 40 > 104.0
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** For oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

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

[#] Revised by the sponsor.

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

[#] Revised by the sponsor.

B: Tables for Laboratory Abnormalities

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

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

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

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

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

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

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

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

10.7. Appendix 7: 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

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

Adults of any age with the following conditions **are at increased risk** of severe illness from the virus that causes COVID-19[b]::

- Cancer
- Chronic kidney disease
- COPD
- Heart conditions, such as heart failure, coronary artery disease or cardiomyopathies
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (BMI of 35 kg/m^2 or higher but < 40 kg/m^2)
- Severe Obesity (BMI ≥ 40 kg/m^2)
- Pregnancy
- Sickle cell disease
- Smoking
- Type 2 diabetes mellitus

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

- Asthma (moderate-to-severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension or high blood pressure
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
- Neurologic conditions, such as dementia
- Liver disease

---

[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. Updated 02 November 2020.

[b] The list of underlying medical conditions is not exhaustive and only includes conditions with sufficient evidence to draw conclusions.

- Overweight (BMI > 25 kg/m^2, but < 30 kg/m^2)
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC AA refVal=https%3A%2F%2Fwww.cdc.gov%2 Fcoronavirus% 2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Accessed: 19 July 2020.

10.8. Appendix 8: 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:

[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

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)
☐ Phlebitis ☐ Lupus
☐ Inflammatory bowel disease ☐ Myeloproliferative disorders
☐ Diabetes mellitus ☐ Hyperlipidemia
☐ Hypertension ☐ Dehydration
☐ Other significant medical co-morbidities or risk factors for DVT, specify:

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

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

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

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)
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		
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		

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)
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:

10.9. Appendix 9: Thrombotic Events to be Reported as Suspected AESIs

The list of thrombotic events to be reported to the sponsor as AESIs is provided below. Further guidance may become available on thrombotic events of interest.

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

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

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

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

10.10. Appendix 10: Protocol Amendment History

Amendment 6 (01 June 2022)

Overall Rationale for the Amendment: The overall reason for this amendment is to allow flexibility to stop enrollment in the sub-study of seronegative participants earlier due to the increasing challenges of recruiting seronegative participants into the sub study. The amendment also removes the interim analysis after the first vaccination at 28 days post dose 1 of the main study. The primary analysis will now include both post dose 1 and post dose 2 data together as the primary analysis. In alignment with other VAC31518 protocols an exclusion criterion was added for TTS and HITT.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for the Study Design 5.2 Exclusion Criteria 9.2 Sample Size Determination	Modify language regarding enrollment targets for seropositive and seronegative participants to allow flexibility to stop enrollment early for seronegative participants in the sub study.	There are increasing challenges in the ability to recruit seronegative participants.
5.2 Exclusion Criteria	A history of TTS or HITT have been added to the exclusion criteria.	To align with other Ad26. COV2.S protocols.
1.1 Synopsis 3 Objectives and Endpoints	Removed the seroconversion objective from the main study and included responder information in the humoral response endpoint for the main study and sub study.	Simplification and clarification of the humoral response objective and endpoint.
1.1 Synopsis 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.5 Planned Analyses	The interim analysis at 28 days post dose 1 has been removed from the protocol, and language to allow additional interim analyses was added.	This interim analysis at 28 days post dose 1 will no longer be performed, but instead the primary analysis will include post dose 1 and post dose 2 data. However, additional analyses may be performed to help facilitate decision making for future studies or regulatory submissions; therefore, language to allow for these additional analyses has been added.
2.3.1 Risks Related to Study Participation	Text has on the relationship of Heparin-induced Immune Thrombotic Thrombocytopenia and TTS has been added.	New updated IB issued with new risk language around TTS.
1.1 Synopsis 8.1 Immunogenicity Assessments	The last sentence in the footnotes of the immunogenicity assessment table was removed.	This footnote was added in Amendment 3 to cover the circumstance of a participant becoming unblinded due to testing outside the protocol.
9.4.1 General Considerations	Added text stating that samples obtained after SARS-CoV-2 infection will not be included in the per protocol immunogenicity analysis set.	Clarification
10.2 Appendix 2: Clinical Laboratory Tests	Combined the columns for serology testing.	Remove redundancy.

Section number and Name	Description of Change	Brief Rationale
11 REFERENCES	Updated IB reference to Edition 6 (2022) and throughout the protocol.	New updated IB issued.
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and clarifications were noted.

Amendment 5 (30 November 2021)

Overall Rationale for the Amendment: The overall reason for this amendment is to clarify that hematology assessment will be assessed pre- and post-vaccination in all of the participants in both the main and sub study. In addition, exploratory endpoints have been updated or added in both the main and sub study to include analysis against emerging variants due to the evolving nature of the COVID-19 virus.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Included neutralization and S-ELISA or equivalent assay analysis of emerging variants in the exploratory objectives for the main and sub study. An additional exploratory endpoint has been added to the main and sub study to access hematology laboratory parameters pre- and post-vaccination.	Due to the evolving nature of the COVID-19 virus. The exploratory objective was missing in the previous version of the protocol.
1.1 Synopsis 8.1 Immunogenicity Assessments	Added ELISA as an additional exploratory assay to the immunogenicity assessments. Also added analysis of emerging variants to SARS-COV-2 VNA.	To align with the addition of the exploratory objective of binding antibody assessment against emerging variants and addition of analysis of emerging variants via VNA.
2 INTRODUCTION	Wording about collaboration with Operation Warp Speed has been removed.	BARDA is not funding the COV3003 study.
8 STUDY ASSESSMENTS AND PROCEDURES	Nasal swab kit has been removed from the list of supplies provided to the investigator.	Nasal swab kits are not provided to the investigator in this study.
10.2 Appendix 2: Clinical Laboratory Tests	Included the timepoints when serum/plasma samples are being collected for coagulation studies and clarified that all participants in the main and sub-study will be assessed for these hematology parameters.	Clarification

Section number and Name	Description of Change	Brief Rationale
1.4.3 Participant with a Suspected AESI 8.3.6.1 Thrombosis and Thrombocytopenia Syndrome	Removed the requirement for laboratory assessments for diagnosis for suspected thrombotic event or TTS.	This allows the sites flexibility to make treatment decisions prior to any laboratory assessments.
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and unclarities were noted.

Amendment 4 (3 August 2021)

Overall Rationale for the Amendment: The mechanism for the rare thrombosis with thrombocytopenia syndrome (TTS) events that have been reported after vaccination with Johnson & Johnson's Ad26.COV2.S vaccine is not known. Examining gene expression in blood cells may inform on the inflammation signals and pro-thrombotic signaling pathways triggered by Ad26.COV2.S that can predispose for TTS. Gene expression profiles will be generated from blood obtained from clinical trials to provide insights into putative signaling pathways that may predispose for TTS and that are triggered by Ad26.COV2.S. Whole blood RNA will be sampled on early timepoints after vaccination with Ad26.COV2.S at different dose levels, examining if the innate gene expression patterns are dose dependent. In addition, serum samples collected at early timepoints can inform on systemic cytokines and chemokines and lipid mediators of innate activation to complement the transcriptome analysis. To further characterize the innate, pro-inflammatory and other relevant (eg, pro-thrombotic) responses to the Ad26.COV2.S vector to better understand a possible risk to TTS events, an additional sub study consisting of 40 seronegative and 20 seropositive participants to Groups 1, 3, 5 and 6 has been added to the study. This sub study will obtain blood samples at additional timepoints for additional analyses of transcriptome and serum innate responses as outlined above to further explore the mechanism of these TTS events.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schema for Participants in the Sub Study 1.4.2 2-dose Vaccination Schedule for Participants in the Sub Study 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Study Design 4.2 Scientific Rationale for Study Design 8 STUDY ASSESSMENTS AND PROCEDURES 8.1 Immunogenicity Assessments 9.2 Sample Size Determination 9.4 Statistical Analyses 9.4.4 Exploratory Endpoint(s) 9.5 Planned Analyses 10.2 Appendix 2: Clinical Laboratory Assessments	A sub study has been added which will include an additional 40 participants per group to investigate the mechanism of action leading to the possible risk to TTS events.	To gain insight into the potential mechanism of TTS.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Updated the endpoint text in the main study objectives from "examining immune response in vaccinated individuals after natural infection" to individuals after "breakthrough infection".	Clarification
5.2 Exclusion Criteria	Exclusion criterion 20 has been updated with a note that seropositive participants are not excluded from entering into the sub study.	Both seronegative and seropositive subjects will be enrolled in the sub study.
2.3.1 Risks Related to Study Participation 7.1 Discontinuation of Study Vaccination 8.2.1 Physical Examinations 10.1 Abbreviations and Definitions	Text has been added regarding the increased risk of Guillain-Barre Syndrome (GBS) following use of the Ad26.COV2.S vaccine. GBS has also been added to the list of reasons for the discontinuation of the Ad26.COV2.S vaccine.	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.
1.1 Synopsis 9.5 Planned Analyses	Clarified up to what day the primary safety and immunogenicity analyses will be performed.	Clarification
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and unclarities were noted.

Amendment 3 (23 June 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is to move the Day 85 sampling timepoint (28 days post-dose 2) to Day 71 (14 days post-dose 2) in order to align across VAC31518COVID studies. This amendment also updates the amount of blood volume needed (from 12 mL to 15 mL) to be collected at baseline and for AESI evaluations due to the increased volume of blood needed to isolate serum/plasma for the coagulation related assays in the study. An additional exclusion criterion for participants with a history of capillary leak syndrome has also been added.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.4.1 2-dose Vaccination Schedule 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Study Design 9.1 Statistical Hypotheses 9.2.1 Immunogenicity 9.5 Planned Analyses 10.2 Appendix 2: Clinical Laboratory Assessments	Move the sampling timepoint from 85 days post first vaccination (28 days post-dose 2) to 71 days post first vaccination (14 days post-dose 2).	To align the post-dose 2 immunological assessment across studies, to occur 14 days post-dose 2.

Section number and Name	Description of Change	Brief Rationale
1.4.1 2-dose Vaccination Schedule 1.4.3 Participants with a Suspected AESI 8 STUDY ASSESSMENTS AND PROCEDURES	The blood volume collected for clinical lab blood samples collected at baseline and for AESIs has been increased from 12 mL to 15 mL.	Clarification on the blood volume to be collected in the event of a suspected AESI.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Vaccination	Additional exclusion criterion and reason for discontinuation of study vaccination have been added that excludes/discontinues participants from the study or further vaccination who have a history of capillary leak syndrome or experience this event after the first study vaccination.	Based on emerging postmarketing safety data.
1.1 Synopsis 8.1 Immunogenicity Assessments	A footnote has been added to the serology table in the synopsis and Table 4 describing the risks to participants who seek serological testing outside the study.	Due to a risk of a participant becoming unblinded through antibody testing outside the protocol.
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and unclarities were noted.

Amendment 2 (10 May 2021)

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

In addition, the blood volume for SARS.CoV.2 serology has been reduced and the exclusion criterion excluding employees and family members from participating in the study has been added back into the protocol per health authority request.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.4.1 2-dose Vaccination Schedule 1.4.3 Participants with a Suspected AESI 2.3.1 Risks Related to Study Participation 2.3.3 Benefit-Risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Study Design 6.8 Prestudy and Concomitant	TTS will be considered an AESI. Follow-up assessments will be performed in the event of a suspected AESI. In addition, blood samples will be collected for a baseline assessments of platelet count and storage for future coagulation-related testing.	Emerging data following use of the Ad26.COV2.S vaccine under emergency use authorization in the US suggest an increased risk of thrombosis combined with thrombocytopenia, with onset of symptoms approximately 1-2 weeks after vaccination. Therefore, additional reporting and data collection procedures are implemented to follow-up thrombotic events and

Section number and Name	Description of Change	Brief Rationale
Therapy 7.1 Discontinuation of Study Vaccination 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.4 Clinical Laboratory Assessments 8.3 Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, 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 9.4.3 Secondary Endpoint(s) 10.2 Clinical Laboratory Tests 10.3.6 Safety Monitoring Committees Structure 10.4 Appendix 4: Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.4.5 Procedures 10.8 Appendix 8: TTS AESI Form 10.9 Appendix 9: Thrombotic Events to be Reported as AESIs		thrombocytopenia and identify cases of TTS.
1.4.1 2-dose Vaccination Schedule	The volume of blood taken for SARS.CoV.2 serology has been reduced from 3.5mL to 2.5mL.	For consistency across COVID protocols.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion excluding employees and family members of the investigator or sponsor from the study has been reintroduced.	Per health authority request.
10.2 Clinical Laboratory Tests	Added a clinical laboratory test table to the appendix.	For consistency across COVID protocols.
Throughout the protocol	Minor grammatical, formatting, spelling changes or clarifications were made.	Minor errors and unclarities were noted.

Amendment 1 (8 March 2021)

Overall Rationale for the Amendment: The main purpose of this amendment is the removal of the Placebo arms of the study, as placebo control is considered not required for end-of shelf-life investigation. Furthermore, after consideration of additional COV2001 study results, dose groups of 9×10^{10} vp, 7×10^{10} vp, and 3.5×10^{10} vp Ad26.COV2.S were added and the 1-dose regimen was removed, resulting in 6 dose-groups, each receiving 2 doses.

Section Number and Name	Description of Change	Brief Rationale
Protocol Title 1.1 Synopsis 2 INTRODUCTION 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.1 Study Vaccines Administered 6.6 Continued Access to Study Vaccine After the End of the Study 9.2.1 Immunogenicity	Placebo arms have been removed.	Placebo control is considered not required for end-of shelf-life investigation
1.1 Synopsis 2.1 Study Rationale 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.3 Justification for Dose 6.1 Study Vaccines Administered 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.2.1 Immunogenicity 9.4.2 Primary Endpoint(s)	Dose groups of 9×10^{10} vp, 7×10^{10} vp and 3.5×10^{10} vp Ad26.COV2.S were added and the 1-dose regimen was removed, resulting in 6 dose-groups, each receiving 2 doses.	New insights after consideration of additional COV2001 study results.
1.1 Synopsis 6.6 Continued Access to Study Vaccine After the End of the Study	Added language that allows participants in groups not meeting non-inferiority to receive a booster dose.	To ensure that participants in groups who received a dose level that did not meet non-inferiority would be eligible to receive a licensed/authorized dose.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.3 Measures to Minimize Bias: Randomization and Blinding 6.6 Continued Access to Study Vaccine After the End of the Study 7.1 Discontinuation of Study Vaccination 9.5 Planned Analyses	Clarification of procedures for unblinding of study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study.	To ensure that if participants become eligible to receive an authorized/licensed COVID-19 vaccine, they are aware of the potential options and ramifications, including the lack of safety data on receiving two different COVID-19 vaccines.
1.1 Synopsis 4.1 Overall Design 9.4.5 Other Analyses	Updated the type of safety information that should be shared with the IDMC from "ongoing" to "significant" safety information.	To clarify type of safety data that will be shared with the IDMC.
1.4.1 2-dose Vaccination Schedule	Clarified in footnote r that the site should report the 2nd vaccination date in the eCOA portal at Visit 4 to ensure that the appropriate diary is visible in the electronic diary. Added to footnote 6 that a valid SARS-CoV-2 test within 28 days of screening was acceptable. Clarified in footnote j that if the participant has acute illness or body temperature ≥38.0°C/100.4°F 24 hours prior to planned vaccination, the vaccination can be rescheduled	Clarifications
1.4.1 2-dose Vaccination Schedule 4.1 Overall Design	Additional blood draw added pre-vaccination at Day 57. Added SARS-Cov-2 serology as a separate sample collection.	Evaluates a longer timepoint after 1 dose. Aliquots for this testing cannot be taken from samples planned for humoral immunity analyses.
5.1 Inclusion Criteria	Redundant text in Criterion 5 stating participants with comorbidities increasing their risk for severe COVID-19 except for smoking was removed. Added the word "female" to Criterion 7 for clarification. Added footnote to inclusion Criterion 6 about the use of condoms as an acceptable contraceptive barrier. Adjusted inclusion Criterion 4 to BMI <35	Mentioned twice in the Criterion. Alignment with other Phase 3 protocols. Alignment with other Phase 3 protocols. To allow less restrictions for enrollment.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy 7.1 Discontinuation of Study Vaccination	Added to Criterion 4 that a substantial immunosuppressive steroid dose is defined as ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent. Therefore, the specification of '(>10 days)' when referring to the chronic use of systemic corticosteroids has been removed from the exclusion criterion 4 and aligned throughout.	Alignment with other Phase 3 protocols.
5.2 Exclusion Criteria 6.8 Prestudy and Concomitant Therapy	Clarified in Criterion 9 that investigational drug includes drugs for prophylaxis of COVID-19. Also clarified that the use of investigational immunoglobulin (Ig) and monoclonal antibodies or convalescent serum are not allowed during the study.	Alignment with other Phase 3 protocols.
5.2 Exclusion Criteria	Updated text to be more specific about the type of blood products used for treatment in Criterion 7. Exclusion criterion 14 deleted: There is no restriction on enrollment of participants that are employees of the investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor. Clarification on definition of diabetes in Criterion 20.	Alignment with other Phase 3 protocols. Clarification
7.2 Participant Discontinuation/Withdrawal From the Study	Clarified that a participant that withdrawals consent will be offered an optional safety visit.	Clarification
8 STUDY ASSESSMENTS AND PROCEDURES	Removed reference to home visits Removed reference to molecular testing for the presence of SARS-CoV-2 infection within 4 days before vaccination,	The study is not operationally set up for home visits
9.4.3 Secondary Endpoint(s)	Removal of the text that SAEs and MAAEs are collected on the full FAS.	Redundant with the previous paragraph.
10.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	Adjusted wording regarding 'permanently sterile'	Alignment with ICF risk language
Throughout the protocol	Minor editorial adjustments for clarification, grammatical, formatting, or spelling changes were made.	Clarification, grammatical, formatting, or spelling correction

11. REFERENCES

1. Agrawal AS (2016), Tao X, Algaissi A, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Hum Vaccin Immunother. 2016;12(9):2351-2356.

2. American Society of Hematology. COVID-19 resources (2021). Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia). https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Accessed: 27 April 2021.

3. Anywaine Z (2019), Whitworth H, Kaleebu P, et al. Safety and Immunogenicity of a 2-Dose Heterologous Vaccination Regimen With Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data From a Phase 1 Randomized Clinical Trial in Uganda and Tanzania. J Infect Dis. 2019;220(1):46-56.

4. Arepally GM, Padmanabhan, A. Heparin-induced thrombocytopenia: a focus on thrombosis. Arterioscler Thromb Vasc Biol. 2021;41:141–152.

5. Barouch DH (2013), Liu J, Peter L, et al. Characterization of humoral and cellular immune responses elicited by a recombinant adenovirus serotype 26 HIV-1 Env vaccine in healthy adults (IPCAVD 001). J Infect Dis. 2013:207(2);248-256.

6. Barouch DH (2018), Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet. 2018;392(10143):232-243.

7. Berry JD (2004), Jones S, Drebot MA, et al. Development and characterisation of neutralising monoclonal antibody to the SARS-coronavirus. J Virol Methods. 2004;120(1):87-96.

8. Bisht H (2004), Roberts A, Vogel L, et al. Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. Proc Natl Acad Sci USA. 2004;101(17):6641-6646.

9. Bolles M (2011), Deming D, Long K, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-12215.

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

11. British Society for Haematology. Guidance produced from the Expert Haematology Panel (EHP) focussed on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT) (2021). https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine 20210407.pdf. Version 1.3; 7 April 2021. Accessed: 27 April 2021.

12. Buchholz UJ (2004), Bukreyev A, Yang L, et al. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. Proc Natl Acad Sci USA. 2004;101(26):9804-9809.

13. Bukreyev A (2004), Lamirande EW, Buchholz UJ, et al. Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet. 2004;363(9427):2122-2127.

14. Centers for Disease Control and Prevention (2021e). Cases of cerebral venous sinus thrombosis with thrombocytopenia after receipt of the Johnson & Johnson COVID-19 Vaccine. 13 April 2021. https://emergency.cdc.gov/han/2021/han00442.asp. Accessed: 27 April 2021.

15. Center for Disease Control and Prevention (2020b). Coronavirus Disease 2019 (COVID-19) Symptoms of Coronavirus. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed: 18 September 2020.

16. Centers for Disease Control and Prevention (2020c). Coronavirus disease 2019 (COVID-19). Groups at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC AA refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.htmlAccessed 19 Jul 2020.

17. Centers for Disease Control and Prevention (2021I). Reproductive Health: Contraception. https://www.cdc.gov/reproductivehealth/contraception Accessed 1 March 2021.

18. Chan JF (2015), Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev. 2015;28(2):465–522.

19. Chen N (2020), Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.

20. Chen Z (2005), Zhang L, Qin C, et al. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol. 2005;79(5):2678-2688.

21. Chin J (1969), Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol. 1969;89(4);449-463.

22. Colby DJ (2020), Sarnecki M, Barouch DH, et al. Safety and immunogenicity of Ad26 and MVA vaccines in acutely treated HIV and effect on viral rebound after antiretroviral therapy interruption. Nat Med. 2020;26(4):498-501.

23. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536-544.

24. Cyranoski D (2020). The biggest mystery: what it will take to trace the coronavirus source. Nature News 2020; doi: 10.1038/d41586-020-01541-z.

25. Deming D (2006), Sheahan T, Heise M, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 2006;3(12):e525.

26. Dong Y (2020), Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16. pii: e20200702. [Epub ahead of print]

27. European Centre for Disease Prevention and Control (2020b). Factsheet for health professionals on coronaviruses. https://www.ecdc.europa.eu/en/factsheet-health-professionals-coronaviruses. Accessed 21 September 2020.

28. European Commission (1998) 98/463/EC: Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community.

29. Faber M (2005), Lamirande EW, Roberts A, et al. A single immunization with a rhabdovirus-based vector expressing severe acute respiratory syndrome coronavirus (SARS-CoV) S protein results in the production of high levels of SARS-CoV-neutralizing antibodies. J Gen Virol. 2005;86(Pt 5):1435-1440.

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

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

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

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

34. Investigator's Brochure (2022): Ad26.COV2.S (VAC31518), Edition 6.0. Janssen Vaccines & Prevention B.V (May 2022).Janssen Vaccines & Prevention B.V. Data on file.

35. Johns Hopkins CSSE (2020). Coronavirus COVID-19 Global Cases. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 19 July 2020.

36. Kapikian AZ (1969), Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969:89(4);405-421.

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

38. Kohl KS (2007), Walop W, Gidudu J, et al./The Brighton Collaboration Local Reaction Working Group for Swelling at or near Injection Site. Swelling at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007:25(31);5858-5874.

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

40. Li Q (2020), Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382:119-1207.

41. Lu R (2020), Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-574.

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

43. Milligan ID (2016), Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia ankara-vectored ebola vaccines: a randomized clinical trial. JAMA. 2016:315(15);1610-1623.

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

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

46. Mutua G (2019), Anzala O, Luhn K, et al. Safety and Immunogenicity of a 2-Dose Heterologous Vaccine Regimen With Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data From a Phase 1 Randomized Clinical Trial in Nairobi, Kenya. J Infect Dis. 2019;220(1):57-67.

47. Sadoff J (2020), Le Gars M, Shukarev G, et al. Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. medRxiv 2020; doi: https://doi.org/10.1101/2020.09.23.20199604.

48. Salisch NC (2019), Izquierdo gil A, Czapska-casey DN, et al. Adenovectors encoding RSV-F protein induce durable and mucosal immunity in macaques after two intramuscular administrations. NPJ Vaccines. 2019;4:54.

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

50. Stephenson KE (2020), Wegmann F, Tomaka F, et al. Comparison of shortened mosaic HIV-1 vaccine schedules: a randomised, double-blind, placebo-controlled phase 1 trial (IPCAVD010/HPX1002) and a preclinical study in rhesus monkeys (NHP 17-22). Lancet HIV. 2020; doi: 10.1016/S2352-3018(20)30001-1. Erratum in: Lancet HIV. 2020 Feb 28.

51. Streiff MB. Pathogenesis and Management of Thrombosis with Thrombocytopenia Syndrome (TTS). Centers for Disease Control & Prevention Advisory Committee on Immunization Practices (ACIP) meeting 23 April 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04-23/02-COVID-Strieff-508.pdf. (accessed 18 May 2021).

52. Subbarao K (2004), McAuliffe J, Vogel L, et al. Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. J Virol. 2004;78(7):3572-3577.

53. Sui J (2005), Li W, Roberts A, et al. Evaluation of human monoclonal antibody 80R for immunoprophylaxis of severe acute respiratory syndrome by an animal study, epitope mapping, and analysis of spike variants. J Virol. 2005;79(10):5900-5906.

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

55. US Department of Health and Human Services (1998). Office for Human Research Protections - OHRP Expedited Review Categories. 1998. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categoriesof-research-expedited-review-procedure-1998/index.html. Accessed 18 September 2020.

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

57. US Food and Drug Administration (2020a). COVID-19: Developing Drug and Biological Products for Treatment or Prevention. Guidance for Industry. May 2020. https://www.fda.gov/media/137926/downloadAccessed 13 November 2020.

58. US Food and Drug Administration (2020b). Development and Licensure of Vaccines to Prevent COVID-19. Guidance for Industry. June 2020. https://www.fda.gov/media/139638/download. Accessed 13 November 2020.

59. van der Fits L (2020), Bolder R, Heemskerk-van der Meer M, et al. Adenovector 26 encoded prefusion conformation stabilized RSV-F protein induces long-lasting Th1-biased immunity in neonatal mice. NPJ Vaccines. 2020 [provisionally accepted for publication]

60. Widjojoatmodjo MN (2015), Bogaert L, Meek B, et al. Recombinant low-seroprevalent adenoviral vectors Ad26 and Ad35 expressing the respiratory syncytial virus (RSV) fusion protein induce protective immunity against RSV infection in cotton rats. Vaccine. 2015;33(41):5406-5414.

61. World Health Organization (2005a). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed 21 September 2020.

62. World Health Organization (2020c). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 06 October 2020.

63. World Health Organization (2004). WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October 2004. https://www.who.int/csr/resources/publications/WHO CDS CSR ARO 2004 1/en/. Accessed 21 September 2020..

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

65. Yang ZY (2004), Kong WP, Huang Y, et al. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. Nature. 2004;428(6982):561-564.

66. Zahn R (2012), Gillisen G, Roos A, et al. Ad35 and Ad26 vaccine vectors induce potent and cross-reactive antibody and T-cell responses to multiple filovirus species. PLoS ONE. 2012;7(12):e44115.

67. Zhang H (2004), Wang G, Li J, et al. Identification of an antigenic determinant on the S2 domain of the severe acute respiratory syndrome coronavirus spike glycoprotein capable of inducing neutralizing antibodies. J Virol. 2004;78(13):6938-6945.

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

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

70. Zhou T (2004), Wang H, Luo D, et al. An exposed domain in the severe acute respiratory syndrome coronavirus spike protein induces neutralizing antibodies. J Virol. 2004;78(13):7217-7226.

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

INVESTIGATOR AGREEMENT

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

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study 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	19-Sep-2022 07:49:10 (GMT)	Document Approval