Janssen Research & Development

Statistical Analysis Plan

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

Protocol VAC31518COV3006; Phase 2

VAC31518 (JNJ-78436735)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Main Change	Rationale
1.0	11Feb2022	Not Applicable	Initial release
2.0	21Apr2022	- Deletion of Part2 - Modifications per Clinical Trial Protocol amendment 3 - Clarifications on subgroup and subgroup analyses - Minor clarifications on AE reporting	- Major changes are expected for Part 2 - Align with Clinical Trial Protocol amendment 3 - Some small subgroups were pooled, and some subgroups analyses are not needed - Clarifications
3.0	12Jul2022	- Correction per Clinical Trial Protocol amendment 3 in Section 5.9 - Clarifications in Section 5.1	- Align with Clinical Trial Protocol amendment 3 - Clarifications for programming derivation
4.0	28Nov2022	- Correction per Clinical Trial Protocol amendment 4 - Modify PPI definition and derivation (to remove PPI2) - Add further output by SARS-CoV-2 Status at Baseline	- Align with Clinical Trial Protocol amendment 4 - Only define one PPI population including all subjects eligible at study entry - Clarifications for programming derivation
5.0	06Sep2023	- Remove the use of MSD results to derive the serostatus at baseline - Add sensitivity analysis on S-ELISA, excluding samples after a 2-fold increase in N-ELISA concentrations is detected - Add shift table for laboratory parameters	- MSD was not fit for purpose at the time of PA and therefore the data were not used to derive the serostatus at baseline. The same approach is then taken for FA, and MSD-4plex data will be reported descriptively as part of the exploratory assessments- Additional analysis excluding subjects with potential SARS-COV-2 infection - Further explore laboratory result changes over time

1. INTRODUCTION

This statistical analysis plan (SAP) specifies definitions of analysis sets, key derived variables, and the statistical analysis methods for the planned analyses of safety, reactogenicity, and immunogenicity data in addition to the planned analyses of the study. The SAP (version 4.0) is based on Clinical Trial Protocol VAC31518COV3006 (CTP) Amendment 4. Previously, this study was designed to comprise Part 1 and Part 2, wherein Part 2 included the Extension Cohort of vaccine naïve participants for evaluation of the dose level and dose regimen selected after review of the data in Part 1. Per CTP amendment 4, Part 2 will no longer be conducted. This SAP therefore refers to Part 1 only. Data from participants who solely received placebo based on CTP Amendment 1 will only be listed. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures and listings) will be provided in a separate document, the Data Presentation Specifications (DPS). This SAP will be finalized prior to the database lock for the primary analysis. After the database lock, separate SAP document(s) may be written as needed to cover specific unplanned analyses that cannot be documented elsewhere (e.g. in the DPS document).

1.1. Objectives and Endpoints

Part 1: Objectives and Endpoints

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

Secondary and Exploratory Objectives and Endpoints for Part 1

Secondary	
• To assess the humoral immune response to 3 dose levels of Ad26.COV2.S (2.5×10^{10} vp, 1.25×10^{10} vp or 0.625×10^{10} vp) and regimens in all study groups at all blood collection timepoints.	• Serological response to vaccination measured by binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (e.g, S protein) as measured by ELISA (or equivalent assay), and/or • Serological response to vaccination measured by neutralizing antibody titers to SARS-CoV-2 (VNA).
• To assess the safety and reactogenicity of Ad26.COV2.S administered IM as a booster in adolescent participants (Groups 1-3).	• Solicited local and systemic AEs for 7 days post-booster. • Unsolicited AEs for 28 days post-booster. • MAAEs from the booster until 6 months post-vaccination.
• To evaluate the humoral immune response in adolescent participants who receive a booster dose during the study, pre-boost and at selected time points post booster vaccination (Groups 1-3).	• Serological response to vaccination measured by binding (S-ELISA and/or equivalent assay) and/or neutralizing (VNA) antibody titers

Exploratory	
• To examine the immune response in vaccinated adolescents after SARS-CoV-2 infection.	• Confirmation of SARS-CoV-2 infection by molecular testing. (1) • SARS-CoV-2 neutralizing titers in serum measured by a VNA. (1) • SARS-CoV-2-binding antibodies measured by ELISA (or equivalent assay): Analysis of antibodies binding to the SARS-CoV-2 S and/or N protein. (1) • Analysis of gene expression by ribonucleic acid (RNA) transcript profiling in adolescents. (1)
• To assess the correlation between the binding antibodies (S-ELISA) and neutralizing antibody (VNA) titers to SARS-CoV-2 at selected timepoints.	• Correlation between ELISA (S-ELISA; EU/mL, or equivalent assay) and VNA (wtVNA(1) and/or psVNA) titers at selected timepoints.
• To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms in adolescents.	• The number of adolescents with molecularly confirmed COVID-19. (1) • Presence and severity of COVID-19 signs and symptoms as measured by the Symptoms of Infection with Coronavirus-19 (SIC).
• To assess for the occurrence of asymptomatic SARS-CoV-2 infection. • For Asymptomatic case definition: See CTP Section 10.9.3	• Serologic conversion between baseline (Day 1; pre-vaccination) and selected timepoints post-vaccination using an ELISA and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 N protein • The number of asymptomatic participants with a SARS-CoV-2 positive molecular test.

Exploratory	
• To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.	• Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA or equivalent assay. (1)
• To assess the impact of the Ad26.COV2.S vaccine on the incidence of co-infections with SARS-CoV-2 and other respiratory pathogens in adolescents who have received Ad26.COV2.S during the study.	• Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in nasal swab samples from adolescents with a symptomatic infection. (1)
• To assess the presence of SARS-CoV-2 variants during a confirmed COVID-19 episode in adolescents. • To assess SARS-CoV-2 viral load during a confirmed COVID-19 episode in adolescents.	• Identification of SARS-CoV-2 variants by sequencing of nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode. (1) • Analysis of SARS-CoV-2 viral load (via qRT-PCR) in nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode. (1)
• To further explore the humoral immune responses in participants who have received Ad26.COV2.S.	Exploratory analyses may include the following assays: <u>Humoral Immune Response:</u> • SARS-CoV-2 neutralization as assessed by VNA. • Adenovirus neutralization as measured by VNA. (1) • Analysis of neutralizing and binding antibodies(1) against emerging SARS-CoV-2 virus lineages. • Functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass and IgG isotype, antibody glycosylation, and assessment of antibody repertoire. (1) • Analysis of antibodies to S, N, and the receptor binding domain (RBD) of the SARS-CoV-2 S protein, and surface proteins of other coronaviruses. (1) • Epitope-specificity characterization of antibodies. (1) • Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma. (1) • Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model. (1) • Seroresponse rates according to different responder definitions.

(1) May be considered as potential assessment for analyses after the primary analysis is performed.

1.2. Study Design

This is a randomized, observer-blind, pivotal Phase 2 study in healthy adolescents from 12 to 17 years of age. The safety, reactogenicity, and immunogenicity of Ad26.COV2.S in a 1- and 2- active dose (56-day interval) vaccination regimen will be evaluated.

The study will descriptively compare the immune responses measured by S-ELISA (and potentially VNA) in adolescents versus the immune responses measured in young adults from study VAC31518COV3001 (after administration of 1 dose of Ad26.COV2.S) or VAC31518COV3009 (after administration of 2 doses of Ad26.COV2.S) and between study groups in VAC31518COV3006.

Previously, this study was designed to comprise Part 1 and Part 2, wherein Part 2 included the Extension Cohort of vaccine naïve participants for evaluation of the dose level and dose regimen selected after review of the data in Part 1. Per CTP amendment 4, Part 2 will no longer be conducted. The study therefore consists of a Dose Selection Cohort to select the most appropriate dose level and regimen for adolescents of 12 to 17 years of age.

The COV3006 study evaluates different dose regimen (1 or 2 vaccinations) and dose levels of $2.5x10^{10}$ vp and lower in participants from 12 to 17 years of age. The 2.5×10^{10} vp has been tested before, in study VAC31518COV2001. A single dose of Ad26.COV2.S at 2.5×10^{10} vp was administered to a cohort of participants 16 to 17 years of age (33 participants received active vaccine or placebo in a blinded manner, 10:1 ratio). Immunogenicity and safety data in adolescents 16 to 17 years of age and adults from COV2001 were evaluated by an IDMC and the Medicines and Healthcare products Regulatory Agency who allowed a continuation of evaluation in participants of 12 to 15 years of age.

In Part 1 (since CTP amendment 2), a target of approximately 300 adolescents, seronegative for SARS-CoV-2 antibodies at baseline will be enrolled to receive 2 vaccinations in the primary vaccination regimen (56-day interval). This primary vaccination regimen will contain 1 or 2 active vaccinations, 1st vaccination with active vaccine for all and second with either active vaccine with the same dose level as 1st or placebo. In this way different doses and schedules (1 or 2 vaccination regimen with active vaccine) will be explored. In Part 1, per CTP amendment 1, some subjects were also randomized to receive placebo only (and were withdrawn by CTP amendment 2).

Since CTP amendment 2, the study starts with a Dose Selection Cohort (Part1), where the participants will be randomly assigned in a 1:1:1:1:1:1 ratio to 1 of 3 study arms to receive one active vaccination of Ad26.COV.2 (either 2.5×10^{10} vp per 0.25 mL dose volume, 1.25×10^{10} vp, or 0.625×10^{10} vp) followed by placebo in a 1-(active) dose regimen (Groups 1, 2 and 3, respectively), or 1 of 3 study arms to receive the same dose level of 2.5×10^{10} vp (per 0.5 mL dose volume), 1.25×10^{10} vp, or 0.625×10^{10} vp in a 2-(active) dose (56-day interval) regimen (Groups 4, 5 and 6, respectively). Each study group will contain approximately 50 participants. Since CTP amendment 3, approximately 70% will be 12 to 15 years of age and approximately 30%, 16 to 17 years of age. Adolescents will be unblinded to the primary vaccination regimen at 6 months after the first vaccination. Also, participants in Groups 1-3 will be given a booster vaccination as of 6 months after the last vaccination with active vaccine. The booster dose level will be 2.5×10^{10} vp per 0.5 mL. Participants in Groups 4-6 will be not given a booster vaccination in the study.

The vaccination schedule for Part 1 is displayed in Table 1.

As a part of the COVID-19 program safety oversight, the IDMC will review the data on an ongoing basis, in addition to two study-specific predefined IDMC analyses.

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

Group	N[a,b,c]	Vac 1 Day 1	Vac 2 Day 57	Vac 3 Day 184
1	50	2.5×10^{10} vp (0.25 mL)	Placebo	2.5×10^{10} vp (0.5 mL)
2	50	1.25×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
3	50	0.625×10^{10} vp	Placebo	2.5×10^{10} vp (0.5 mL)
4	50	2.5×10^{10} vp (0.5 mL)	2.5×10^{10} vp (0.5 mL)	none
5	50	1.25×10^{10} vp	1.25×10^{10} vp	none
6	50	0.625×10^{10} vp	0.625×10^{10} vp	none

N = number of participants; n/a = not applicable; SDL = selected dose level; Vac = vaccination; vp = virus particles.
a Not more than 70% of males or females should be randomized in each age group
b All participants must be seronegative for SARS-CoV-2 antibodies at baseline.
c Approximately 30% of participants should be between 16 to 17 years age and approximately 70% should be between 12 to 15 years of age.

Not more than 70% males or females will be randomized in each age group. The randomization will be stratified by sex and age group. In Part 1, screening will aim to ensure participants are seronegative at baseline for SARS-CoV-2 antibodies.

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

2. STATISTICAL HYPOTHESES

There is no formal hypothesis testing in Part 1.

Descriptive statistics will be reported to descriptively compare vaccine immunogenicity in adolescents from this study VAC31518COV3006 versus vaccine immunogenicity in selected young adults (18 to 25 years of age) from study VAC31518COV3001 or study VAC31518COV3009 (with similar baseline characteristics to the participants expected to be enrolled in this study – see Section 6.11), and between study groups in VAC31518COV3006.

All enrolled participants were seronegative for SARS-CoV-2 antibodies when screened with local rapid finger-prick serology testing at baseline. However, the primary analysis results have shown that many participants were retrospectively established to be SARS-COV-2 seropositive at baseline by central testing with Nucleocapsid (N) and/or Spike (S) -based serology. Therefore data from SARS-COV-2 seropositive young adult (18 to 25 years of age) selected from other Phase 3 studies will be used to compare vaccine immunogenicity in seropositive at baseline adolescents from this study.

3. SAMPLE SIZE DETERMINATION

The sample size for Part 1 shall enable selection of appropriate doses and regimens. Decision making on the optimal regimen will primarily take into account safety and reactogenicity data. Non-binding guidelines on dose and regimen selection are described in Section 5.9.1.

Additionally, any available immunogenicity data from Part 1 participants and data from other Janssen clinical trials of Ad26.COV2.S will also be considered.

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

Table 2: 90% Two-Sided CI for Possible Observed Rate of Adverse Events

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

In Part 1, a target of approximately 300 adolescents, seronegative for SARS-CoV-2 antibodies at baseline will be enrolled.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Enrolled	All participants who sign the main ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	The Full Analysis Set will include all participants with at least one vaccine administration documented.

Analysis Sets	Description
Per Protocol Immunogenicity Set (PPI)[a]	The Per Protocol Immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding data from participants with major protocol deviations expected to impact the immunogenicity outcomes (see details in Section 6.3). In addition, samples obtained after missed vaccinations, samples obtained from participants after SARS-CoV-2 infection (if confirmed by molecular testing or non-S-ELISA [or equivalent assay]), occurring during the study after randomization (if applicable), after other SARS-CoV-2 vaccination outside the study, and samples obtained outside pre-defined time windows will be excluded from the analysis set (see details in Sections 5.1.4 and 6.3).

[a] If a participant is vaccinated out of window due to a study pause, this will not by default be a reason for excluding this participant from the PPI. Participants who were seronegative by local serology finger-prick test on Day 1 prior to study entry but were determined to be seropositive at baseline by central N- or S- serology testing will also be included (as the results from those assessments are not known prior to randomization).

5. STATISTICAL ANALYSES

5.1. General Considerations

Details of the vaccine schedules associated to the primary vaccine regimen will be provided in the data presentation specification (DPS) document. Vaccination schedule have 2 components:

- Primary Vaccine Regimen (1-active dose or 2-active dose)
- Booster Vaccination (i.e. after unblinding)

Unless specified otherwise, analyses outputs will be produced by age group (12 to 15, 16 to 17, and overall). Where applicable, output will include results by dose level (1-active dose regimen and 2-active dose regimen combined) to report the post-dose 1 period.

All safety and immunogenicity data after a participant has received any other SARS-CoV-2 vaccine not part of the protocol will not be tabulated. Those data will be in listings.

A baseline (or reference) value will be defined as the value of the last available assessment prior to the first vaccination on Day 1, unless specified otherwise.

Unless otherwise stated, safety analyses will be conducted on the FAS, Immunogenicity analyses on the PPI.

5.1.1. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study vaccination. Unless specified otherwise, safety assessments at all visits will be assigned a day relative to this date. In addition, safety assessments occurring after vaccination 2 in the primary regimen period and those occurring after the booster vaccination date will also be assigned a day relative to those dates.

Study Day is defined as follows:

- *Study Day=visit date-date of Day 1 + 1; if visit date ≥ date of Day 1 (date of first vaccination).*
- *Study Day=visit date-date of Day 1; if visit date < date of Day 1 (date of first vaccination).*

Relative day (relday), the number of days in the analysis time point will be defined as:

- *relday=visit date-reference date+1* for visits on or after the reference date,
- *relday=visit date-reference date* for visits before the reference,

where the reference date equals the date of vaccination 1 or 2, or the date of booster vaccination.

5.1.2. Study Phases

To assess study phases, in case the time of the vaccination is missing, the time will be imputed with 00:00 before applying the phase and period derivation rules. When the time of the first vaccination is missing and it occurred on the same day as the randomization, the time of vaccination will be imputed with the time of randomization.

The safety analysis results will be presented by phase/period.

5.1.3. Phase Definitions

The phases in the Part 1will be constructed as described in Table 3.

Table 3: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the IC form	One second prior to start of post dose 1 period
Post-dose	2	Post-dose 1	1	Date and time of first vaccination	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) 23:59:59 on 28 days after the first vaccination (23:59:59 of day of vaccination + 28 days) d) One second prior to date and time of second vaccination e) One second prior to date and time of Booster Vaccination f) One second before date and time of another viral vaccination outside the study
Follow-up 1	3			One second after Post-dose 1 period end	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) One second prior to 6 months after first vaccination (vaccination date + 6 mths) d) One second prior to date and time of second vaccination e) One second prior to date and time of Booster Vaccination f) One second before date and time of another viral vaccination outside the study
Post-dose	2	Post-dose 2	2	Date and time of second vaccination	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) 23:59:59 on 28 days after the second vaccination (23:59:59 of day of vaccination + 28 days) d) One second prior to date and time of Booster Vaccination e) One second before date and time of another viral vaccination outside the study

Table 3: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Follow-up 2	4			One second after Post-dose 2 period end	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) One second prior to 6 months after second vaccination (vaccination date + 6 mths) d) One second prior to date and time of Booster Vaccination e) One second before date and time of another viral vaccination outside the study
Long term follow-up	5			One second after Follow-up 1 if only 1 dose was administered, and one second after Follow-up 2 if the 2 doses were administered	Minimum of: a) Maximum of 23:59:59 at the date of last contact (for early discontinuation) and 23:59:59 at the date of last visit b) 23:59:59 at the date of data base cut-off date in case of interim analysis a) One second prior to date and time of Booster Vaccination b) One second before date and time of another viral vaccination outside the study c) One second prior to end of the study visit
Post-dose	2	Post-dose 3 (will be referred as Post-booster in the output)	3	Date and time of Booster Vaccination	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) 23:59:59 on 28 days after the Booster Vaccination d) One second before date and time of another viral vaccination outside the study
Booster follow-up 1	6			One second after Post-dose 3 period end	Minimum of: a) 23:59:59 at the date of last contact (for early discontinuation) b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) One second prior to 6 months after Booster Vaccination d) One second before date and time of another viral vaccination outside the study
Booster long term follow-up	7			One second after booster follow-up 1	Minimum of: a) Maximum of 23:59:59 at the date of last contact (for early discontinuation) and 23:59:59 at the date of last visit b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) One second before date and time of another viral vaccination outside the study d) One second prior to end of the study visit

Table 3: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Follow-up other vaccine	8			Date and time of viral vaccination outside the study	Minimum of: a) Maximum of 23:59:59 at the date of last contact (for early discontinuation) and 23:59:59 at the date of last visit b) 23:59:59 at the date of data base cut-off date in case of interim analysis c) Date and time of end of the study visit

5.1.3.1. Other Follow-up Visits

The following other time intervals will be derived for safety data summary as shown in Table 4.

Table 4: Other Time Intervals

Time Intervals	From	To
Up to Day 85 (only for the primary analysis)	Date and time of first vaccination	Maximum of: a) Post-dose 1 end date b) Follow-up 1 end date c) Post-dose 2 end date
Primary Vaccination Period	Date and time of first vaccination	Maximum of: a) Post-dose 1 end date b) Follow-up 1 end date c) Post-dose 2 end date d) Follow-up 2 end date e) Long term follow-up
Booster Vaccination Period	Date and time of Booster Vaccination	Maximum of: a) Post-dose 3 end date b) Booster follow-up 1 end date c) Booster long term follow-up
Entire Study	Date and time of first vaccination	Maximum of: a) Primary Vaccination Period end date b) Booster Vaccination Period end date

5.1.4. Visit Windows

Referring to CTP Section 1.3 per protocol visit windows will be taken into account for the analysis, where applicable.

For immunogenicity-related data analysis, the PPI derivation (see details in Section 6.3) will be based on the rules which follows:

- Samples obtained after a second vaccination administered outside the time window of the planned day +/- 8 days will be excluded; as well as after a booster vaccination administered outside the time window of the planned day -30 days to +180 days (Groups 1-3).
- Samples obtained outside the following pre-defined time windows will also be excluded:
  - Pre-vaccination for sampling planned on vaccination day
  - Sampling planned day after last vaccination +/- 2 days, if the planned day is 7 days after last vaccination (e.g Day 8 post booster vaccination if given per CTP amendment 3)

- Sampling planned day after last vaccination +8 / -4 days, if the planned day is 14 days after last primary regimen vaccination (i.e. 14 days after dose 2)
- Sampling planned day after last vaccination +/- 8 days, if the planned day is 28 days or 56 days after last primary regimen vaccination (i.e. Day 29 and Day 57 post-dose 1)
- Sampling planned day between 10 and 36 days after booster vaccination, if the planned day is 14 or 28 days after booster vaccination (i.e. sampling post booster vaccination, as given per CTP amendment 3 or amendment 4)
- Sampling planned day after last vaccination +/- 30 days, if the planned day >3 months after last vaccination.

Time windows may be redefined prior to unblinding if the number of samples excluded as per the definitions above are too numerous. No time windows apply for Early Exit visit sampling.

The sample closest to the target day (at noon) will be selected, if two or more samples meet the PPI definition in the pre-defined time windows.

If some participants have undergone sampling at different timepoints than those required per CTP amendment 4 because they followed a different CTP amendment version, data from those different timepoints may be presented separately or pooled together with the most appropriate timepoint per CTP amendment 4 (e.g. all samples planned at 14 or 28 days after booster vaccination will be reported together).

5.1.5. Pooling Algorithm for Analysis Centers

Data will be pooled across the different centers.

5.1.6. Analyses by Groups and Pooled Across Groups

In Part 1, summary outputs will be produced with pooled study groups that received the same dose up to D57 in addition to the analyses planned for each study group separately, unless specifically indicated otherwise. Immunogenicity analyses will be carried out by SARS-CoV-2 serostatus at baseline (in participants with a baseline result by central N- and S- serology testing, in PPI or FAS) and 'overall' (all participants, in PPI or FAS).

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized by study group (where applicable) and overall:

- Participants screened
- Participants randomized
- Participants in FAS
- Participants in PPI
- Participants who completed the study
- Participants who discontinued vaccination
- Participants who terminated study prematurely

- Reasons for termination of study
- Participants who discontinued study

Listings of participants will be provided for the following categories:

- Participants vaccinated and not randomized
- Participants randomized and not vaccinated
- Participants who discontinued study
- Participants who discontinued vaccination
- Participants who were unblinded during the study period.

Participants with major protocol deviations will be identified prior to database lock and will be summarized by category. Details are available in Section 6.5.

5.3. Extent of Exposure

The number and percentage of participants who receive study vaccination, as well as the number of days between the 2nd and 1st vaccination, the number of days between the Day 29 sample and the 1st vaccination, and the number of days between the Day 71 sample and the 2nd vaccination will be summarized by vaccination schedule. The number and percentage of participants by visit (Day 1, Day 29, Day 57, Day 71, etc) will similarly be summarized.

Study vaccination compliance will be summarized descriptively by vaccination schedule. Details are available in Section 6.7.

5.4. Primary Endpoints Analysis

5.4.1. Definition of Endpoint(s)

Safety and Reactogenicity Endpoints

Section 5.7.1 provides AE definitions associated with primary and secondary safety and reactogenicity endpoints.

The primary endpoints to assess the safety and reactogenicity are:

- Solicited local and systemic AEs for 7 days post-dose 1 and 2.
- Unsolicited AEs for 28 days post-dose 1 and 2.
- MAAEs from the first vaccination until 6 months post-last dose.
- SAEs, AESIs (TTS and MIS-C) and MAAEs leading to discontinuation from the first vaccination until the end of the study.

Humoral Immune Response Endpoints

S-ELISA (or equivalent assay, e.g. MSD) or VNA will be used as primary humoral immune response endpoint to assess the serological response to vaccination in Part 1:

- Serological response to vaccination as measured by S-ELISA (ELISA Units/mL [EU/mL]) or equivalent assay, or VNA titers at 28 days post-dose 1, and 14 days post-dose 2.

For S-ELISA or equivalent assay (e.g. MSD), wild type, and pseudovirion VNA, a sample is defined as positive if its value is strictly greater than the LLOQ (>LLOQ).

5.4.2. Estimands

Not applicable.

5.4.3. Analysis Methods

Unless otherwise specified, participants will be analyzed according to the vaccination regimen they actually received (i.e. not according to the planned vaccination regimen). Participants who receive Ad26.COV2.S 2.5×10^{10} vp per 0.5 mL will be analyzed together with those who received Ad26.COV2.S 2.5×10^{10} vp per 0.25 mL. Those who receive a 2-active dose regimen will be analyzed in the 2-active dose regimen at the dose level of the 1st active dose actually received.

Safety and Reactogenicity Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by phase. Selected tables will also be presented by subgroups (age group, sex, SARS-CoV-2 serostatus at baseline [or in seronegative subgroup only if there are less than 5% of seropositive subjects], BMI group, race and ethnicity), as defined in Section 5.8.5. In addition, for selected tables, tabulations pooled by vaccination dose will also be provided. Details are provided in Section 5.6 and Section 5.7.1.

The rate of occurrence of specific local and systemic adverse events will used to identify the maximum dose with acceptable reactogenicity compared to the rate observed in young-adult participants of study COV3001. Details are provided in Section 5.9.1.

Humoral Immune Response Endpoints

The immunogenicity analyses will be performed on the PPI population.

Immunogenicity results will be presented by vaccination schedule, by SARS-CoV-2 by serostatus at baseline [or in seronegative subgroup only if there are less than 5% of seropositive subjects], and overall, per scheduled time point using the pre-defined visit windows. Selected immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and will be shown in the graphs using different colors and symbols) and on key other subgroups (sex, age group and also on BMI, race and ethnicity for the primary endpoint) as defined in Section 5.8.5. Samples taken outside of the allowed window (included in the FAS analysis and excluded from the output in the analysis on PPI) will be included and flagged in the listings as results not included in the PPI analyses.

Categorical variables will be summarized with a frequency table showing counts and percentages. Continuous variables will be summarized using the following statistics, as appropriate: Number of observations, geometric mean, arithmetic mean (mean), 95% confidence interval (CI) for the mean, standard deviation (SD), standard error (SE), median, quartiles (Q1 and Q3), minimum and maximum. Binary variables will be summarized using the following statistics: number of observations, percentages, and Exact Clopper-Pearson 95% CIs (where appropriate).

Data listings, participant profiles and/or participant narratives may be provided as appropriate.

5.5. Secondary Endpoint(s) Analysis

5.5.1. Definition of Endpoint(s)

The following endpoints will assess the humoral immune response to 3 dose levels of Ad26.COV2.S (2.5×10^{10} vp, 1.25×10^{10} vp or 0.625×10^{10} vp) in all participants (Part 1) in all study groups, at all blood collection timepoints:

- Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA (or equivalent assay),

  and/or
- Neutralizing antibody titers to SARS-CoV-2 as measured by VNA titers.

5.5.2. Estimand(s)

Not applicable

5.5.3. Analysis Methods

The analysis methods are described in Section 5.8.1.

5.6. Exploratory Endpoint(s) Analysis

Definitions and details about the analysis methods for exploratory humoral immunogenicity endpoints are given in Section 5.8.1. Some of the exploratory immunogenicity endpoints mentioned in this section will only be considered as potential assessment for post-hoc analysis after the primary analysis is performed, as described in Section 1.1.

Immune response in vaccinated adolescents after natural SARS-CoV-2 infection.

- Confirmation of SARS-CoV-2 infection by molecular testing.
- SARS-CoV-2 neutralizing titers in serum measured by a VNA.
- SARS-CoV-2-binding antibodies measured by ELISA: Analysis of antibodies binding to the SARS-CoV-2 S and/or N-protein. Infections in this study were identified either by a positive PCR test or by N serology seroconversion (N-ELISA result from negative to positive) [see Section 5.8.3]. In order to censor data from participants following a potential SARS-CoV-2 infection not identified by the pre-defined infection rule, a sensitivity analysis will be performed on vaccine-induced humoral responses (binding and neutralizing antibody titers) for the PPI at the time of the final analysis. In this sensitivity analysis, data from participants from the time point where a >= 2-fold increase in N-ELISA titers is observed in any two consecutive available time points during the study will be censored.

Correlation (at selected timepoints)

- ELISA (S-ELISA; EU/mL, or equivalent assay) and VNA (wtVNA and/or psVNA) titers
  - For S-ELISA and wtVNA correlation.
  - For S-ELISA and psVNA correlation.
- ELISA (S-ELISA; EU/mL, or equivalent assay) titers at baseline and its fold increase from baseline.

Occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms in adolescents

- The number of adolescents with molecularly confirmed COVID-19.
- Presence and severity of COVID-19 signs and symptoms as measured by the Symptoms of Infection with Coronavirus-19 (SIC).

Occurrence of asymptomatic SARS-CoV-2 infection

- Serologic conversion between baseline (Day 1; pre-vaccination) and selected timepoints post-vaccination using an ELISA and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 N protein
- The number of asymptomatic participants with a SARS-CoV-2 positive molecular test.

For asymptomatic case definition, see CTP (Section 10.9.3).

Impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity

- Analysis of antibodies binding to coronaviruses other than SARS-CoV-2 by ELISA or equivalent assay.

Impact of the Ad26.COV2.S vaccine on the incidence of co-infections with SARS-CoV-2 and other respiratory pathogens in adolescents who have received Ad26.COV2.S during the study.

- Analysis of broad respiratory pathogens panel in the nasal swabs collected during a confirmed COVID-19 episode and in nasal swab samples from adolescents with a symptomatic infection.

SARS-CoV-2 variants during a confirmed COVID-19 episode in adolescents

- Identification of SARS-CoV-2 variants by sequencing of nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode.

SARS-CoV-2 viral load during a confirmed COVID-19 episode in adolescents

- Analysis of SARS-CoV-2 viral load (via qRT-PCR) in nasal swabs and/or saliva samples (as available) collected during a confirmed COVID-19 episode.

Explore the humoral immune response in participants who have received Ad26.COV2.S.

Exploratory analyses may include the following:

- SARS-CoV-2 neutralization as assessed by VNA.
- Adenovirus neutralization as measured by VNA.
- Functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass and IgG isotype, antibody glycosylation, and assessment of antibody repertoire.
- Analysis of antibodies to S, N, and the RBD of the SARS-CoV-2 S protein, and surface proteins of other coronaviruses.

- Epitope-specificity characterization of antibodies.
- Cytokine profiling: Analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the serum or plasma.
- Passive transfer: Analysis of immune mediators correlating with protection against experimental SARS-CoV-2 challenge in a suitable animal model.

5.7. (Other) Safety Analyses

5.7.1. Adverse Events

5.7.1.1. Definitions

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local events (pain/tenderness, erythema, and swelling at the injection site) and systemic events (fatigue, headache, nausea, and myalgia, fever) for which the participant or parent(s)/caregiver(s) is specifically questioned, and which are noted by participants or parent(s)/caregiver(s) in their reactogenicity diary. Unsolicited AEs are all AEs for which the participant or parent(s)/ caregiver(s) is not specifically questioned.

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 first vaccination until 6 months after each vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF. Solicited administration site symptoms will by definition be considered as related to the study vaccine.

The following adverse events of special interest (AESI) will be collected in this study:

- Thrombosis with Thrombocytopenia Syndrome (TTS), defined as:
  - Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in CTP Section 10.14 and in Section 6.10
  - Thrombocytopenia, defined as platelet count below 150,000/µL.
- Multisystem Inflammatory Syndrome in Children (MIS-C), defined as:
  - An individual aged <21 years presenting with fever[a], laboratory evidence of inflammation[b], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2)

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

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

organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND

- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

The AESI will be reported from the moment of vaccination until the end of the study/early withdrawal. An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine cases of TTS.

5.7.1.2. Severity Criteria

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on the version of September 2007 (US DHHS FDA CBER 2007), included in Sections 6.8 and 6.9, Toxicity Grading Scale in Adolescents (12 to 17 Years of Age).

For AEs not identified in the grading table, the guidelines in CTP (Section 10.4.3) will be applied.

The severity of solicited signs and symptoms are graded in the reactogenicity diary by the participant based on the severity assessment provided in the reactogenicity diary and then verified by the investigator using the Toxicity Grading Scale. The severity of a measured event is derived from the diameter [for erythema and swelling] or the temperature measurements [for fever].

5.7.1.3. Analysis of Adverse Events

The number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated.

Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (administration site, systemic) and preferred term.

For solicited AEs, the following tables will be provided: summary, by worst severity grade, at least grade 3, related (systemic only), at least grade 3 related, time to onset (in days) from the start of each vaccination period and duration (in days) for most frequent events (>5%) and body temperature. Note: Duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference dates are the start dates of all prior vaccination periods (i.e. the prior vaccination dates for dose 1, dose 2 and/or Booster).

For unsolicited AEs, the following tables will be provided: summary table (including SAE, AESIs, MAAEs, MAAEs leading to study discontinuation, fatal outcome, and discontinuation), all events, most frequent (>5%), at least grade 3, related, at least grade 3 related, and SAE. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

Selected tables will be repeated by SARS-CoV-2 by serostatus at baseline [or in seronegative subgroup only if there are less than 5% of seropositive subjects], and overall.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study due to an AE, experience a SAE, or AESI.

5.7.1.4. Phase Allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period.

Step 1: Allocation of events to the periods

Adverse events in the SDTM data base are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

- In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.
- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. In case of a completely missing start date, the event is allocated to the first active vaccination regimen phase (post dose 1 period), except if the end date of the AE falls before the start of the first active vaccination regimen phase (post dose 1 period).

Step 2: Combination of events

Overlapping/consecutive events are defined as events of the same participant with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1. If overlapping/consecutive events start in one of the following periods – Screening or post dose extension (i.e. non-active periods) – followed by an AE in – post-dose period (active period) – they are allocated to their respective periods and are considered as separate events.
2. In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the AdaM data base but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
3. In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the AdaM data base but are assigned the same onset, vaccination regimen period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
4. In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.
2. In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.
3. Time is not considered when determining overlap of events.

5.7.1.5. Missing Data

Missing data will not be imputed. Participants who do not report an event/concomitant medication will be considered as participants without an event/concomitant medication. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade but will be considered as not reported for the analysis of at least grade 3.

5.7.2. Laboratory, Vital Signs and Physical Examination

Coagulopathy laboratory values will be listed. A listing of all other laboratory values will be made, restricted to participants with at least one laboratory abnormality.

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

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics.

Abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the FDA table in Section 6.8 and in Section 6.9.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from ‘abnormally low’ at baseline to ‘abnormally high’ post baseline (or vice versa) is also considered emerging. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.
- The abnormalities ‘abnormally low’ and ‘abnormally high’ are considered equally important, i.e. if a participant has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

- Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.
- If a laboratory value falls within the grading as specified in the grading table but also within the local lab normal limits, the value is considered as normal.

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the CTP will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

Change from baseline in laboratory results (shift table based on toxicity grade) will be summarized by timepoint post vaccination.

A listing of participants with fever according to the FDA grading table will also be provided. In addition, temperature measurements (whether obtained from the diary or from on-site assessments) will be allocated to predefined temperature intervals (from 37.5° C until 40°C, in steps of half degree increments; e.g. <37.5, 37.5-<38, 38-<38.5, … >40), and the worst temperature reported over the first 7 first days after a vaccination (Day1 to Day8, from any of the diary or the on-site assessments) will be tabulated by intervals.

5.8. Other Analyses

5.8.1. Immunogenicity Analyses

The analysis of immunogenicity will use the PPI set. Immunogenicity analyses will also be done on the FAS (participants who became infected during the study will be analyzed as a subgroup and shown in the graphs using different colors and symbols). Data will be analyzed by vaccination schedule, age group. Key immunogenicity assay results will also be analyzed for the subgroups defined in Section 5.8.5.

Data will be presented by scheduled time point. For the PPI analysis, samples taken outside of the allowed window will be excluded from the tables and graphs (but will be included in the listings and clearly marked as results not included in the PPI analyses). For the FAS analysis, samples taken outside of the allowed window will be included. Key immunogenicity assay data from other studies, which are used to benchmark results from this study, will also be generated. Reference to the respective study will be added to those tables and graphs.

Note: analyses that are potentially unblinding at the individual participant level (e.g. graphs showing individual data tied to COVID-19 infection status, especially when the number of COVID-19 infections is low and/or when time of infection is indicated) will be carried out after official unblinding of the trial, or will be carried out exclusively on specific groups (or other clearly defined subgroups) after these are unblinded. Alternatively, prior to unblinding, these analyses can be performed in a completely blinded manner (e.g. tables with only a single column pooling all regimens).

5.8.1.1. Parameters

The following humoral immune responses may be measured (Table 5). However, not all assays might be available for all immunogenicity analyses covered by this SAP. Some of the exploratory immunogenicity endpoints mentioned in this section will only be considered as potential assessment for post-hoc analysis after the primary analysis is performed, as described in Section 1.1. Further information on which assays will be analyzed in each of the analyses, will be included in the corresponding DPS documents.

Table 5: Summary of Humoral Immunogenicity Assays

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

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

5.8.1.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values below the lower limit of quantification (LLOQ) or limit of detection (LOD, if available instead of LLOQ) will be handled as follows:

- Calculation of geometric mean and median:
  - values<LLOQ are imputed with LLOQ/2.
- Calculation of fold increases from baseline:
  - values <LLOQ are imputed with LLOQ.

Values above the upper limit of quantification (ULOQ) will be handled as follows:

- Calculation of geomean and median:
  - Values>ULOQ are imputed with ULOQ.
- Calculation of fold increases from baseline:
  - Values >ULOQ are imputed with ULOQ.

5.8.1.3. Handling of Changes in Assay Status Throughout the Study Conduct

In case of changes in assay status, from "qualified" to "validated", the LLOQ and ULOQ are likely to change as well. If this should happen, then the SDTM database will contain records pertaining to the assay in the qualified status and records pertaining to the validated status, and the LLOQ and ULOQ values will also differ.

The statistical analysis will use the LLOQ and ULOQ values associated with the validated assay and will retrospectively apply these on all the data pertaining to the assay, including the data obtained while the assay status was "qualified". This may imply that data received, statistically analyzed, and presented at an earlier time may change. Graphical displays will show the eventually used LLOQ and ULOQ values. Graphs and tables will have an additional footnote, that reflects the assay status.

5.8.1.4. Immunogenicity Against the Insert

5.8.1.4.1. Humoral assays

The seroresponse rate of S-ELISA (or equivalent assay, e.g. MSD), and the VNA will be reported as the proportion of participants with either:

- a baseline sample value of less than or equal to the lower limit of quantitation (LLOQ; [≤LLOQ]) and a postbaseline sample strictly greater than the LLOQ (>LLOQ), or
- a baseline sample value strictly greater than the LLOQ (>LLOQ) and a postbaseline sample value representing an at least 4-fold (≥4-fold) increase from the baseline sample value.

In addition, the following definition of seroresponse rate of the VNA (and possibly S-ELISA or equivalent assay e.g. MSD) will be reported as an exploratory endpoint: the proportion of participants with at least 4-fold increase from the baseline sample value, where a baseline sample value of less than or equal to the lower limit of quantitation will be set to LLOQ for the analysis.

For S-ELISA and VNA (both wild-type virus and pseudovirion expressing S protein, as available) assays, the following results will be calculated: N, geometric mean and corresponding 95% CI of

the actual values and fold increases from baseline and from pre-dose 2 or pre-dose 3 (for time points after dose 2 and time points post booster, respectively) will be tabulated and graphically presented.

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the $\log_{10}$ transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

Actual values are tabulated and shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay. In addition, GMT (VNA) or GMC (S-ELISA or equivalent assay, e.g. MSD) plots over time, combining the regimens in one graph (without individual participant dots) will also be generated.

Participant profiles of the actual values over time will be graphically presented. In the graphs, original values will be displayed on the $\log_{10}$ scale. Reverse distribution curves of the actual values will be provided for selected time points. Further details and/or updated rules will be provided in the DPS.

The ratio of binding antibodies (S-ELISA or equivalent assay, e.g. MSD) to wild type VNA, and the ratio of binding antibodies (S-ELISA or equivalent assay, e.g. MSD) to pseudovirion expressing S protein VNA will be calculated for each time point. Values <LLOQ will be imputed with LLOQ for the calculation of the ratios. In addition, the ratio of the fold increase from baseline in binding antibodies (S-ELISA or equivalent assay, e.g. MSD) to the fold increase from baseline in wild type VNA, and the ratio of the fold increase from baseline in binding antibodies (S-ELISA or equivalent assay, e.g. MSD) to the fold increase from baseline in pseudovirion expressing S protein VNA will be calculated for each post-baseline time point. Values <LLOQ will be imputed with LLOQ for the calculation of the fold increase ratios. The following statistics will be calculated and tabulated: N, geometric mean and corresponding 95% CI of the ratio. Graphical displays will also be prepared, showing – for each time point – the geometric mean of the ratio and its 95% CI, together with the individual data points (dot plot).

If a similar assay is performed at different analyzing labs, then separate statistical analyses may be performed.

Scatterplots between humoral assay results will be provided for selected time points. These may include but are not limited to:

- Binding antibodies S-ELISA (or equivalent assay) versus VNA (wtVNA and/or psVNA)
- Ad26 VNA versus S-ELISA (or equivalent assay), wtVNA or psVNA (as available)

If a similar assay is performed at different analyzing labs, then the statistical analyses may distinguish between these and provide separate scatterplots for each analyzing lab versus the other assay of interest. These scatterplots will display the values as analyzed for the geometric mean calculations, with values <LLOQ imputed with LLOQ (if an LLOQ is defined) and values >ULOQ imputed with ULOQ (if an ULOQ is defined). The LLOQ and ULOQ cut-off values per assay will

be visualized in the scatterplots. Spearman correlation coefficients will also be provided (one per scatterplot).

Further details and/or updated rules will be provided in the DPS.

5.8.2. COVID-19 Case Monitoring to Detect Imbalances Across Study Groups (Harm Monitoring)

In the absence of a placebo arm, no 'harm monitoring' can be conducted.

5.8.3. COVID-19-like Signs and Symptoms

Procedures to be performed in the event a participant experiences signs or symptoms suggesting possible COVID-19 are detailed in CTP Section 1.3, Schedule of Activities and CTP Section 8.1.2, Procedures in case of COVID-19-like Signs and Symptoms.

The COVID-19-like Signs and Symptoms will be analyses for the participants with a COVID-19 infection. The presence of SARS-CoV-2 infection will be assessed at the study site by molecular testing using the nasal swab sample and also based on SARS-CoV-2 N serology results. It is defined as a SARS-CoV-2 N serology (N-ELISA) change from baseline result from negative to positive, or a positive SARS-CoV-2 PCR-status.

The analyses described in this section will be conducted on the FAS at the time of the final analysis.

The number and percentage of participants with at least one SARS-CoV-2 infection will be tabulated by vaccination schedule.

In the group of participants seronegative at baseline, the number and percentage of participants with at least one positive non-S protein ELISA (e.g., N ELISA), if available, will be tabulated by vaccination schedule.

For each participant with confirmed COVID-19 infection, a narrative will be prepared based on the visit performed 28 days after the onset of COVID-19 signs and symptoms and other selected information from the clinical database, as available:

- participant ID
- vaccination regimen
- sex, race, ethnicity, age, BMI, dates at which vaccinations were received
- pulse oximetry
- physical examination findings based on the visit performed 28 days after the onset of COVID-19 signs and symptoms
- vital signs including body temperature based on the visit performed 28 days after the onset of COVID-19 signs and symptoms
- Humoral immune responses as collected at the planned time points + those obtained from the blood sample taken on the visits performed 3 and 28 days after the onset of COVID-19 signs and symptoms. This information may be presented graphically.

For the analysis of the SIC (Patient Reported Outcomes, PRO) data, the following considerations apply:

- An "episode" is defined as a period in which any symptoms are reported on the SIC, starting from the first day on which symptoms were reported until the first day that the PRO was not completed because the symptoms had resolved (this will be indicated in the SDTM data, with reason for not completing the PRO = "Symptoms resolved" (or similar)) or death
- A symptom (e.g. feeling generally unwell, fatigue, physical weakness, cough, etc.) is assumed to be present on each day the associated Yes/No question is answered "Yes" or the associated severity question has a rating > 0.
- If the PRO was not completed due to the participant being too ill or due to the participant being hospitalized, the symptom will be considered present with maximum severity score. If the PRO was completed due to any other reason, no imputations will be done.

Duration of the episode will be calculated as (episode end date – episode start date) + 1. Duration of each symptom will be calculated as last date of symptom reporting – its first date + 1.

The following analyses will be conducted for confirmed SARS-CoV-2 infection cases:

- At the level of first episodes, the following statistics will be calculated: number of episodes, mean and median duration of episodes (with min, max, q1 and q3), and mean and median number of symptoms reported per episode (with min, max, q1 and q3).
- At the level of the symptoms for each first episode, the following statistics will be calculated: number of participants experiencing the symptom, mean and median duration of each symptom (with min, max, q1 and q3), median (with min, max, q1 and q3) of highest severity of each symptom, median duration of the highest severity of each symptom (with min, max, q1 and q3).
- At the level of the participants, for each episode and each symptom separately, the duration, and minimum and maximum severity scores will be tabulated (as available).

In addition, participant listings will be provided containing the SIC information for each time point. Details about these analyses will be provided in the DPS.

5.8.4. Demographics and Baseline Characteristics

Demographic and baseline variables will be summarized by vaccination schedule and overall for the FAS. Details about demographics and baseline characteristics are provided in Section 6.4.

SARS-CoV-2 Serostatus at baseline will be derived from the S-ELISA, N-ELISA as well as from MSD 4, if available. Seronegative at baseline is defined as negative per S-ELISA and per N-ELISA (values ≤ LLOQ) and, if available, per MSD 4plex S and MSD 4plex N (values ≤ LOD or LLOQ*). Seropositive at baseline is defined as positive per S-ELISA or per N-ELISA (values > LLOQ), or, if available, per MSD 4plex S or per MSD 4plex N (values > LOD or LLOQ*). SARS-CoV-2 Serostatus at baseline will be assigned to 'no baseline' if the S-ELISA or N-ELISA results are missing. Since MSD 4 results were not available by the time of the primary analysis, and the same derivation rules will be applied for the final analysis, SARS-CoV-2 Serostatus at baseline will be derived from the S-ELISA, N-ELISA only.

5.8.5. Definition of Subgroups

Subgroups are defined in as shown in Table 6.

Table 6: Definition of subgroups

Subgroup (at baseline)	Definition
Age Group	• 12-15 years (≥12y to <16y) • 16-17 years (≥16y to ≤17y)
BMI	• underweight (<18.5 kg/m^2) • normal (18.5-<25 kg/m^2) • overweight and obese (>=25 kg/m^2)
Race	• Asian • Black or African American • White • Other ('Multiple[a] or 'Native Hawaiian or other Pacific Islander' or 'American Indian or Alaska Native')
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino
Sex	• Male • Female
SARS-CoV-2 Serostatus	• Positive • Negative

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'.

For safety and immunogenicity analyses, results will at least be analyzed by vaccination schedule and age (at baseline) group.

Safety and immunogenicity subgroup analyses will also be performed for selected summaries by sex, by SARS-CoV-2 serostatus at baseline (or in seronegative subgroup only if there are less than 5% of seropositive subjects), as well as by BMI at baseline, by race, and ethnicity for the primary endpoints. Subgroup analysis will ignore unknown, missing and not reported values, unless otherwise specified.

5.9. Planned and Interim Analyses

The following analyses are planned based on the Part 1 data:

- Regular monitoring of the safety data will be performed by IDMC, which is unblinded to the study data, based on cumulative data available in the database from approximately 6 months after start of recruitment.
- A first IDMC (unblinded) analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 1.
- A second IDMC (unblinded) analysis of Part 1 will be performed on safety and reactogenicity data 28 days post-dose 2.
- Selected sponsor members will also review group unblinded summaries of those two IDMC analyses, as well as of any available immunogenicity data up to 28 days post-dose 1 and up to 14 days post-dose 2.
- 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 prior to the final analysis.

- A primary analysis of safety, reactogenicity and immunogenicity data up to 28 days post-dose 2 will be performed and the selected dose level will be determined for any future pediatric studies. The sponsor will be unblinded at the time of the primary analysis, but the blind will be maintained at a participant and study site level up to the unblinding visit.
- The final analysis will be performed when all participants have completed their last visit in Part 1 or discontinued earlier.

5.9.1. Non-binding Guidelines on Dose and Regimen Selection

Non-binding guidelines on dose and regimen selection were originally defined to determine the most appropriate dose level for Part 2 and any future pediatric studies. However, following the cancellation of Part 2, those guidelines will not be assessed in the context of this study.

Assuming a monotone dose-response on immunogenicity, the maximum dose with acceptable reactogenicity will be selected based on an assessment of the rate of local and systemic Grade 3 adverse events. The assessment of acceptability will take a non-binding dual Go/No-Go framework for each dose into account. The reactogenicity will be compared to the reactogenicity data from young-adult participants of study COV3001 and COV3009. The difference in reactogenicity is flagged as:

- acceptable, if the upper bound of the one-sided 95%-Confidence interval on the rate difference of local and systemic adverse events to the young-adults is below 20%.
- problematic, if the difference is not deemed acceptable and the lower bound of the one-sided 90%-Confidence interval on the rate differences of local and systemic adverse events to the young adults is above 10%, or if any Pyrexia event of Grade ≥3 has been observed on the considered dose.

Above guidelines lead under the assumption of N=50 participants per study group from COV3006 to an observed rate difference of up to ~10% being flagged as acceptable. A difference of ~20% or larger would be flagged as problematic by the considered guidelines. A problematic dose could still be considered as acceptable for continued evaluation based on clinical reasoning.

Reactogenicity is assumed to increase with increasing doses. If a low dose has been deemed as problematic, any higher dose will automatically be deemed as at least as problematic.

Assuming an underlying grade 3 event rate in the COV3001 (or COV3009) comparator group of 20%, the considered guidelines will result in the probabilities of declaring a dose as acceptable or problematic shown in Table 7.

Table 7: Probability to Outcome by Event Rate

Event rate COV3006	Probability of acceptable outcome	Probability of inconclusive outcome	Probability of problematic outcome
20% (Δ=0%)	97.5%	2.4%	0.1%
30% (Δ=10%)	48.2%	44.7%	7.1%
40% (Δ=20%)	4.3%	46.2%	49.5%
50% (Δ=30%)	0.7%	8.5%	91.4%

5.9.2. Data Monitoring Committee (DMC) or Other Review Board

An Independent Data Monitoring Committee (IDMC) has been commissioned to review the safety data of this trial alongside the other COVID-19 trials. Please refer to the IDMC Charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
AESI	Adverse event of special interest
BMI	Body Mass Index
CI	confidence interval
CoV	Corona Virus
COVID-19	Corona Virus Disease 2019
CRF	case report form
CSR	Clinical Study Report
CTP	Clinical Study Protocol
DMC	Data Monitoring Committee
DPS	Data Presentation specifications
DRC	Data Review Committee
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FU	Follow-up
GMC	Geometric mean concentration
GMR	Geometric mean titer ratio (GMT adolescents / GMT young adults)
GMT	Geometric mean titer
ICH	International Conference on Harmonization
ICS	Intracellular Cytokine Staining
IFN-γ / IFN-g	Interferon gamma
IL	Interleukin
ITT	Intent-to-Treat
IU/ml	International units per milliliter
IWRS	interactive web response system
kg	Kilogram
LLOQ	lower limit of quantification
LOD	Limit of detection
m	meter
MAAEs	Medically Attended Adverse Events
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number
NA	Not Applicable
PBMC	peripheral blood mononuclear cell
PD	Pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)

PP	Per Protocol
PPI	Per Protocol Immunogenicity Set
PRO	Patient Reported Outcome
Q1	First quartile
Q3	Third quartile
RNA	Ribonucleic acid
S	Spike
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SIC	Symptoms of Infection with COVID-19
Th1	Helper cell type 1
Th2	Helper cell type 2
TLF	Tables, Listings and Figures
TNF-α / TNF-a	Tumor necrosis factor alpha
ULOQ	Upper limit of quantification
VNA	Virus Neutralization Assay
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not applicable.

6.3. Appendix 3 The Per Protocol Immunogenicity population

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 and occurring on Day 1 or before.

In addition, samples obtained from participants will be excluded from the analysis set:
-a- after major protocol deviations expected to impact the immunogenicity outcomes and occurring after Day 1,
-b- after missed vaccinations,
-c- on or after natural SARS-CoV-2 infection (if confirmed by molecular testing or non-S-ELISA [or equivalent assay]) occurring during the study after randomization (if applicable),
-d- after other SARS-CoV-2 vaccination outside the study, or
-e- outside pre-defined time windows (Section 5.1.4).

In terms of derivation, the samples to consider for analysis on Per Protocol Immunogenicity must meet the following criteria:

Subject level

- **Crit1:** Must be randomized
- **Crit2:** Must be in FAS

- **Crit7:** No major protocol deviations with impact on immunogenicity on or before day 1 excluding Deviation Categories ’85 for sample not in window’, ’87 for sample not stored properly’

Subject data level

Subject data to be excluded on and after the date of any of the following events:

- **Crit11:** seropositive post-Baseline by N-ELISA (value>LLOQ), if seronegative at baseline (as defined in Section 5.8.4)
- **Crit13**: SARS-CoV-2 infection occurring on or after Day 1
- **Crit20**: Major protocol deviations with impact on immunogenicity after day 1 except for deviation categories ‘85’ or ’87’, which includes
    - **Crit21:** post SARS-CoV-2 viral vaccination outside the study occurring after Day 1
    - **Crit22:** Vacc 2 not in D57 +/- 8 days
    - **Crit23:** no Vacc 2, then exclude samples where the sample date>Day57+8.
    - **Crit24:** Vacc 3 not in D184 +180/-30 days post vacc1 – Groups 1, 2, 3
    - **Crit25:** no Vacc 3 (within 180 days post Day 184), then exclude samples where the sample date>Day184+30 – Groups 1, 2, 3

Vacc 2 refers to the 2nd dose of the primary regimen
Vacc 3 refers to booster

Sample level

Samples to be excluded on the date of deviation for ‘85’ or ‘87’ events:

- Crit30: major protocol deviations with impact on immunogenicity deviation categories ‘85’ or ‘87’, that is
    - **Crit31:** D1 sample not in window
    - **Crit32:** D29 sample not in window
    - **Crit33:** Day 57 sample not in window
    - **Crit41:** D1 sample not stored properly (i.e. protocol deviation ‘87’)
    - **Crit42:** D29 sample not stored properly
    - **Crit43:** Day 57 sample not stored properly

    Reference to Vacc 2
    - **Crit34:** Day 71 sample compared to date of Vacc2 not in window
    - **Crit35:** Day 184 sample compared to date of Vacc1 not in window - Groups 1, 2, 3-
    - or Day 184 sample compared to date of Vacc2 not in window - Groups 4, 5, 6-
    - **Crit44:** Day 71 sample not stored properly
    - **Crit45:** Day 184 sample not stored properly

    Reference to Vacc 3=booster
    - **Crit36:** D7 or D14 sample post Vacc3 not in window - Groups 1, 2, 3-
    - **Crit37:** D184 sample post Vacc3 not in window - Groups 1, 2, 3-
    - **Crit46:** D7 or D14 sample post Vacc3 sample not stored properly - Groups 1, 2, 3-
    - **Crit47:** D184 sample post Vacc3 sample not stored properly - Groups 1, 2, 3-

6.4. Appendix 4 Demographics and Baseline Characteristics

Demographic and baseline variables (Table 8) will be summarized by vaccination schedule and overall for the FAS.

Table 8: Demographic Variables

Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of participants in each category.
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple- *If multiple race categories are indicated, the Race is recorded as 'Multiple'-*)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)	
Country	
Region	
SARS-CoV-2 Serostatus at Baseline (No baseline, Positive, Negative)	
Age group: • ≥12y to ≤15y • ≥16y to ≤17y	

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	

6.5. Appendix 5 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong vaccination regimen or incorrect dose
- Other

Major protocol deviations which have a potential impact on immunogenicity will be flagged in the listings.

6.6. Appendix 6 Prior and Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

For all participants, concomitant therapies associated with an SAE will be collected and recorded in the eCRF from the moment of first vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of first vaccination until 6 months after 2nd vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study. The proportion of participants with concomitant medication associated with these SAEs and MAAEs will be tabulated and listed.

For all participants, concomitant therapies such as, but not limited to, analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, and vaccinations will be recorded from the moment of first vaccination until 28 days after administration of study vaccine, and thereafter, pre-dose on the day of any subsequent vaccination and for 28 days after that vaccination. The proportion of participants with concomitant medication will be tabulated by period.

For all participants, other concomitant therapies will also be recorded if administered in conjunction with a confirmed COVID-19 case or with new or worsening AEs reported per protocol requirements outlined in CTP Section 6.8. The proportion of participants with concomitant medication associated with these cases will be tabulated and listed.

Based on their start and stop date, concomitant therapies will be reported in each applicable phase.

If a concomitant therapy record misses components of its start and/or stop dates (time, day and/or month and/or year):

- In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

There will be special attention to any systemic use of analgesics/antipyretics, started within 8 days following each vaccination (00:00 of day of vaccination + 7 days). Following CMCLASCD (ATC/DD codes) will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION). The classes will be added in a footnote in all related tables and listings. For the use of analgesics/antipyretics which are taken on the day of vaccination an

exception is made in case the time is before vaccination. In this case the concomitant medication is also allocated to the post-dose period.

The use of antipyretics with fever will be tabulated and the use of antipyretics on immunogenicity will be tabulated (overall, NSAIDs vs non-NSAIDs).

6.7. Appendix 7 Compliance

Study vaccine compliance will be calculated as follows:

Study vaccine compliance (%) = (actual number of vaccination doses/total number of vaccination doses supposed to be taken) x100.

Compliance will be summarized descriptively by vaccination schedule and age group.

6.8. Appendix 8 Toxicity Grading Scales in Adolescents (12 to 17 Years of Age)

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007) (US DHHS FDA CBER 2007) (Table 9).

Table 9: Tables for Clinical Abnormalities

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

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

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

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.

6.9. Appendix 9 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

The laboratory values provided in the tables below (Table 10 to Table 12) serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered as normal.

Table 10: Tables for Toxicity Grading Scale

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

Table 10: Tables for Toxicity Grading Scale

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	ï€ 1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
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)
International Normalized Ratio (INR)***	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 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.
** "ULN" is the upper limit of the normal range.
***: For INR, the values in the table are based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2014 (version 2.0)

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 forhyperglycemia
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.

Table 11: Ranges to Convert FDA Scale to SI Units

Ranges to convert FDA scale to SI units		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life threatening (Grade 4)
Albumin (g/L)	Hypo-albuminemia	28-31	25-27	<25	
Eosinophils (10^9/L)		0.65-1.5	1.501-5.0	>5.0	
Hemoglobin for male (g/L)		125-135	105-124	85-104	<85
Hemoglobin for female (g/L)		110-120	95-109	80-94	<80
Hemoglobin change from baseline (g/L)		Any decrease – 15	16-20	21-50	>50
Lymphocytes (10^9/L)		0.75-1.0	0.5-0.749	0.25-0.499	<0.25
Neutrophils (10^9/L)		1.5-2.0	1.0-1.499	0.5-0.999	<0.5
Platelets (10^9/L)		125-140	100-124	25-99	<25
Protein (g/L)	Hypo-proteinemia	55-60	50-54	<50	
WBC (10^9/L)	Increase	10.8-15	15.001-20	20.001-25	>25
	Decrease	2.5-3.5	1.5-2.499	1.0-1.499	<1.0

Table 12: Other Conversions

Blood, Serum, or Plasma Chemistries[1]		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)	Conversion factor
Glucose (mmol/L)	Hypoglycemia	3.61-3.83	3.05-3.60	2.50-3.04	<2.50	/18.01477
	Hyperglycemia-Fasting	5.55-6.11	6.12-6.94	>6.94		
	Hyperglycemia-Random	6.11-6.94	6.95-11.10	>11.10		
Blood urea nitrogen (mmol/L)		8.2-9.3	9.4-11.1	>11.1		
Creatinine (µmol/L)		133-150	151-177	178-221	>221	/0.01131
Calcium (mmol/L)	Hypocalcemia	2.00-2.10	1.87-1.99	1.75-1.86	<1.75	/4
	Hypercalcemia	2.62-2.74	2.75-2.87	2.88-3.00	>3.00	/4
Magnesium (mmol/L)	Hypomagnesemia	0.53-0.62	0.45-0.52	0.37-0.44	<0.37	/2.43072
Phosphorus (mmol/L)	Hypophosphatemia	0.74-0.81	0.65-0.73	0.52-0.66	<0.52	/3.09693
Cholesterol (mmol/L)		5.20-5.43	5.44-5.82	>5.82		
Coagulation						
Fibrinogen (µmol/L)	Increase	11.76-14.70	14.71-17.65	>17.65		
	Decrease	4.41-5.88	3.68-4.40	2.94-3.67	<2.94	/34

6.10. Appendix 10 Thrombotic Adverse Events of Special Interest

The list of thrombotic events to be reported to the sponsor as suspected AESIs is provided below:

- 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

[1] Depending upon the laboratory used, reference ranges, eligibility ranges and grading may be split out by sex and/or age.

- 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

6.11. Appendix 11 Selection of Young Adults from Studies COV3001 and COV3009

The selection of young adults from COV3001 and COV3009 for NI comparison to adolescents in COV3006 will be made in 4 steps, with the aim of exact matching on coarsened covariate:

1. Identify all randomized and vaccinated participants (i.e., from the FAS) from study COV3001 and study COV3009 who meet the following criteria:
    - age 18 to 25 years old, included
    - gender was known and defined as male or female.
    - had blood samples collected Day 1 and Day 29 for study COV3001, or Day 1 and Day 71 for study COV3009 not previously analyzed for immunogenicity.
    - have sufficient aliquots in those samples to perform S-ELISA and VNA analyses
    - participants with none of the following criteria:
        - protocol deviations expected to impact immunogenicity
        - HIV positive
        - SARS-CoV-2 infection occurring after Day 1
        - samples post embolic and thrombo event (SMQ)
        - samples obtained after missed vaccinations, or other vaccination
        - samples outside defined visit windows -in days- (Day 1 in [-99,1]; Day 29 in [24,34] for COV 3001 study; Day 71 sample taken in [11,28] days after the second vaccination dose which also had to be in Day 57 defined window [42, 79] for COV 3009 study)

2. Identify baseline characteristics to stratify participants and select similar participants from studies COV3001 and COV3009 than from study COV3006 based on those strata. The baseline characteristics considered are:
    - SARS-CoV-2 serostatus at baseline (positive, negative; missing and unknown will not be considered),
    - sex (male or female; other category, missing, and unknown will not be considered)
    - region (Asia, Europe [EU], Latin America [LATAM], Northern America [NA], Southern Africa [SA]))
    - countries (Asia: Philippines, India, Thailand; EU: Belgium, France, Germany, Spain, United Kingdom; LATAM: Argentina, Brazil, Chile, Colombia, Mexico, Peru; NA: United States; SA: South Africa)

- Race (White, Black or African American, Asian, Others; missing, not reported or unknown will be pooled separately as unknown)
- Ethnicity (Hispanic or Latino, Others; not reported, missing or unknown will not be pooled separately as unknown)

3. The baseline characteristics considered will be ordered based on their expected importance to differentiate immunogenicity response in the different strata.
   In COV3001 study, starting with the most important, the order chosen is:

   1/Serostatus, 2/ Sex, 3/ Region, 4/Country, 5/ Race and 6/Ethnicity

   In COV3009 study, two additional criteria were added for their impact on immunogenicity response:

   A- the number of days between the sample after the second vaccination and the second vaccination, [11,17] and [18,28];
   B- the number of days between the first and second vaccination, [42,49], [50,64] and [65,79].

   Starting with the most important, the order is:

   1/Serostatus, 2/ Criteria A, 3/ Criteria B, 4/Sex, 5/ Region, 6/Country, 7/ Race and 8/Ethnicity

4. For Part 1, the selection of 'matching' participants from study COV3001 (or study COV3009) will be based on the characteristics of the first 100 participants planned to be enrolled in COV3006 Part 1. That is 28 participants from Brazil, 10 from India, 28 from Argentina, and 34 from South Africa. They are in a proportion of 50%/50% male/female and it is assumed that all participants will perform their assessments and vaccination according to protocol. No assumption was made on race and ethnicity, and thus those were assigned to unknown.

   For each study COV3006 participant, starting with the first one randomized, the matching participant in study COV3001 (or study COV3009) will be selected as the one with the latest date of randomization among the participants with the highest Participant Matching Score (PMS). The participant with the latest date of randomization is used so that the participant matching a 3006 participant is randomly selected among all potential participants from study COV3001 (or study COV3009) identified in step 1.

   The PMS between a participant of study COV3006 and of study COV3001 will be derived based on the correspondence between baseline characteristics. Each PMS digit represents a characteristic and has a value 1 or 0, if the two participants compared respectively match or not for that characteristic.

   The PMS will be derived as follows for COV3001:

   ScoreSerostatus = 1 if Serostatus matches between the 2 participants, else it is 0
   ScoreSex = 1 if Sex matches between the 2 participants, else it is 0
   ScoreRegion = 1 if Region matches between the 2 participants, else it is 0
   ScoreCountry = 1 if Country matches between the 2 participants, else it is 0

ScoreRace = 1 if Race matches between the 2 participants, else it is 0
ScoreEthnicity = 1 if Ethnicity matches between the 2 participants, else it is 0
PMS= ScoreSerostatus*10^5 + ScoreSex*10^4 + ScoreRegion*10^3+
ScoreCountry*10^2 + ScoreRace*10 + ScoreEthnicity

The PMS between a participant of study COV3006 and of study COV3009 will be derived based on the scores defined for COV3001 and the scores for criteria A and B defined above. Following the same logic, the ScoreCriteriaA = 1 if CriteriaA matches between the 2 participants, else it is set to 0. However, as criteria B is ordered with 3 categories the following logic will be applied to ScoreCriteriaB:

ScoreCriteriaB = 2 if CriteriaB matches between the 2 participants,
1 if CriteriaB is 1 category apart between the 2 participants,
0 otherwise

The PMS will be derived as follows for COV3009 participants:

PMS= ScoreSerostatus*10^7 + ScoreCriteriaA*10^6 + ScoreCriteriaB *10^5
+ScoreSex*10^4 + ScoreRegion*10^3+ ScoreCountry*10^2
+ ScoreRace*10 + ScoreEthnicity

Category unknown will be coded differently (e.g. category ‘9’) in the study COV3006 than in study COV3001 (or study COV3009) (e.g. category ‘8’) so that a study COV3006 participant with an unknown characteristics will be matched to any study COV3001 participant (or study COV3009) for that characteristic rather than within the unknown characteristic category.

Examples for the study COV3001:

- -If a participant in the study COV3001 matches perfectly a participant in the study COV3006, the PMS is 111111 between those 2 participants, the participant with the highest randomization number in the corresponding strata is selected as the best match.
- -If there is no more participant in the study COV3001 for a given strata, then among the participants with the highest randomization number in the other stratum, the PMS will be the highest if the participants match for all other characteristics. For example, if there are no more participants in the study COV3001 for a specific country, the PMS=111011 is the highest score possible.