Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Phase 3 Study to Evaluate Safety, Reactogenicity, and Immunogenicity of Co-administration of Ad26.COV2.S and Influenza Vaccines in Healthy Adults 18 Years of Age and Older

Protocol VAC31518COV3005; Phase 3

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

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
0.1	Not Applicable	Not Applicable	Initial draft release
0.2	Not Applicable	First review and comments from COV3005 Team	Initial draft release
0.3	Not Applicable	Responses to first review, HA FDA protocol review integration and second review	Initial draft release
0.4	Not Applicable	Responses to second review	Initial draft release
0.5	Not Applicable	Responses to third review	Initial draft release
0.6	Not Applicable		Protocol Amendment 1
0.7	Not Applicable		Clarification for populations and subgroup analyses

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains information needed to perform the complete safety and immunogenicity analysis of the VAC131518COV3005 trial. It describes more technically and with more details the pre-planned analysis for the Primary Analysis and Final Analysis found in the Section 9.4 of the clinical trial protocol (CTP). A Data Presentation Specification Document (DPS) will be available to further detail the statistical outputs that will be generated.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the NI of the humoral immune response of the 4 influenza vaccine strains after concomitant administration of the Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of a seasonal quadrivalent *standard-dose* influenza vaccine administered alone.	• Antibody hemagglutination inhibition (HI) titers as measured by hemagglutinin inhibition (HAI) assay titers (geometric mean titers [GMTs]) against each of the 4 influenza vaccine strains, 28 days after the administration of a seasonal quadrivalent standard-dose influenza vaccine. Success criteria for NI • the upper bound of the 2-sided 95% confidence interval (CI) for the geometric mean titer (GMT) ratio (Control group/co-administration [CoAd] group) lies below 1.5
To demonstrate the NI of the binding antibody response after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine administered alone.	• Antibody titers as measured by S enzyme-linked immunosorbent assay (S-ELISA) titers (GMC), 28 days after administration of Ad26.COV2.S vaccine. Success criteria for NI

Objectives	Endpoints
	• the upper bound of the 2-sided 95% confident interval (CI) for the GMC ratio (Control group/CoAd group) lies below 1.5
Secondary	
To assess the safety and reactogenicity of a single dose of Ad26.COV2.S vaccine when administered separately or concomitantly with a seasonal quadrivalent *high-dose* influenza vaccine in participants aged 65 years and older.	• Solicited local (injection site) and systemic AEs for 7 days after each vaccination. • Unsolicited AEs for 28 days after each vaccination. • SAEs, MAAEs, and AESIs throughout the study. • AEs leading to withdrawal from the study throughout the study.
To assess the safety and reactogenicity of a single dose of Ad26.COV2.S vaccine when administered separately or concomitantly with a seasonal quadrivalent *standard-dose* influenza vaccine in participants aged 18years and older.	• Solicited local (injection site) and systemic AEs for 7 days after each vaccination. • Unsolicited AEs for 28 days after each vaccination. • SAEs, MAAEs, and AESIs throughout the study. • AEs leading to withdrawal from the study throughout the study.
To assess the humoral immune response against each of the 4 influenza vaccine strains after concomitant administration of the Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine versus the administration of a seasonal quadrivalent *high-dose* influenza vaccine administered alone.	• Antibody HI titers as measured by HAI assay titers (GMTs) against each of the 4 influenza vaccine strains, 28 days after the administration of a seasonal quadrivalent *high-dose* influenza vaccine.
To assess the humoral immune response of Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine versus the administration of a seasonal quadrivalent *high-dose* influenza vaccine administered alone.	• Antibody titers as measured by S enzymelinked immunosorbent assay (S-ELISA) titers (GMC), 28 days after administration of Ad26.COV2.S vaccine.
To assess the humoral response to SARS-CoV-2 after the concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone *in COVID-19 vaccine-naïve individuals.*	• Antibody titers as measured by S enzyme-linked immunosorbent assay (S-ELISA) titers (GMC), 28 days after administration of Ad26.COV2.S vaccine.
To assess the humoral response to SARS-CoV-2 after the concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone *in COVID-19 vaccine-naïve individuals.*	• Antibody titers as measured by S enzyme-linked immunosorbent assay (S -ELISA) titers (GMC), 28 days after administration of Ad26.COV2.S vaccine.
To compare seroconversion rates against the 4 influenza vaccine strains after the concomitant	• Seroconversion is defined for each of the 4 influenza vaccine strains at 28 days after the

Objectives	Endpoints
administration of Ad26.COV2.S vaccine and a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine versus a vaccination of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine administered alone.	administration of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine: - HI titer ≥1:40 in participants with a pre-vaccination HI titer of <1:10, or - a ≥4-fold HI titer increase in participants with a pre-vaccination HI titer of ≥1:10.
To assess seroprotection rates against the 4 influenza vaccine strains after the concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine versus a vaccination of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine administered alone.	• Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 28 days after the administration of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine.
Exploratory	
To evaluate the durability of influenza-specific humoral immune responses after concomitant administration of the vaccines versus the influenza vaccine alone.	• GMT: Geometric mean of HI antibodies at Day 181. • Percentages of participants with HI titers ≥1:40 on Day 181.
To evaluate the durability of SARS-CoV-2 specific humoral immune responses after concomitant administration of the vaccines versus the SARS-CoV-2 vaccine alone.	• Antibody GMC by S-ELISA at Day 181 after the administration of Ad26.COV2.S vaccine.
To assess the magnitude and durability of humoral immune responses specific to influenza.	• Serological responses to vaccination as measured by HAI at Day 181 after the administration of influenza vaccine.
To further assess humoral responses to Ad26.COV2.	• Serological response to vaccination, as measured by virus neutralization assay (VNA) (SARS-CoV-2 VNA and/or pseudo virion [ps] VNA expressing S protein) titers. • Adenovirus 26 neutralization responses measured by VNA. • Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass, and IgG isotype. • Correlation between ELISA (S-ELISA) and VNA (wild-type virus [wt]VNA and/or pseudovirion [ps]VNA) titers at selected timepoints.
To explore the humoral responses to Ad26.COV2.S and influenza vaccine based on the SARS-CoV-2 serostatus at baseline (N-serology).	• Serological response to vaccination as measured by S-ELISA antibody concentration 28 days after the administration of Ad26.COV2.S vaccine.

Objectives	Endpoints
	• Antibody GMC by S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine. • Antibody HI titers as measured by HAI assay titers (GMTs) against the 4 influenza strains.
To explore the humoral responses to Ad26.COV2.S and influenza vaccine based on the previous history of COVID-19 vaccination at entry (viral vector vaccine or mRNA vaccine or vaccine naïve).	• Serological response to vaccination as measured by S-ELISA antibody concentration 28 days after the administration of Ad26.COV2.S vaccine. • Antibody GMC by S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine. • Antibody HI titers as measured by HAI assay titers (GMTs) against SARS-CoV-2.

1.2. Study Design

This is a randomized, double-blind, parallel, multicenter, interventional study in healthy (including stable comorbidities) adults ≥18 years of age. In this study, the safety, reactogenicity, and immunogenicity of Ad26.COV2.S co-administered with a seasonal influenza vaccine will be evaluated.

Participants will be randomized in parallel in this study. Participants aged ≥65 will be randomized in a 1:1:1:1 ratio to 1 of 4 groups. Participants aged ≤64 will be randomized in a 1:1 ratio to 1 of 2 groups (Group 1 or Group 2). Efforts will be made to ensure good representation in terms of race, gender, and ethnicity.

Participants will receive Ad26.COV2.S and a seasonal quadrivalent (*standard-dose* or *high-dose*) influenza vaccine either concomitantly on Day 1 and placebo on Day 29 (co-administration groups 1 and 3) or a seasonal quadrivalent (*standard-dose* or *high-dose*) influenza vaccine and placebo on Day 1 and Ad26.COV2.S on Day 29 (control groups 2 and 4) (see table 2 below).

Table 1: Overview of the Groups and Vaccinations

Group	Day 1	Day 29
1 (CoAd group)	Ad26.COV2.S + Q SD influenza vaccine	Placebo
2 (Control group)	Placebo + Q SD influenza vaccine	Ad26.COV2.S
3 (CoAd group)	Ad26.COV2.S + Q HD influenza vaccine	Placebo
4 (Control group)	Placebo + Q HD influenza vaccine	Ad26.COV2.S

CoAd = coadministration; HD = high-dose; Q = quadrivalent; SD = standard-dose.

The seasonal quadrivalent *standard-dose* influenza vaccine (Groups 1 and 2) can be administered to all participants. Age is included as stratification factor for Groups 1 and 2 (≥18 to ≤64 years of age versus ≥65 years of age). The seasonal quadrivalent *high-dose* influenza vaccine (Groups 3 and 4) will only be administered to participants ≥65 years of age.

The previous SARS-CoV-2 vaccination history (Vaxzevria [AstraZeneca], Comirnaty [Pfizer-BioNTech], SpikeVax [Moderna], and Ad26.COV2-S [Janssen]) will be used as second stratification factor during the randomization process. These stratification levels will ensure well-distributed proportional representation of each previous vaccines within each of the 4 study groups.

Enrollment will be monitored weekly for age group and previous vaccination history to ensure sites are enrolling a diverse population of participants and similar proportions of previous vaccines within each group.

Participants can either have received a complete primary vaccination with an authorized/licensed COVID-19 vaccine (completed ≥6 months prior to first study vaccination) or be COVID-19 vaccine-naïve. The type of primary vaccination will be documented and accounted for according to interactive web response system (IWRS) procedures.

The study duration from screening until the last follow-up visit will be approximately 7-8 months. The study comprises screening on Day -28 to 1, vaccination visits on Days 1 and 29 with a 28-day follow-up period after each vaccination. AEs leading to withdrawal, MAAEs, SAEs, and AESIs will be collected throughout the study.

2. STATISTICAL HYPOTHESES

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by vaccine group.

The study is successful if the below objectives are demonstrated:

- NI of the humoral immune response as measured by the HI assay after concomitant administration of Ad26.COV2.S vaccine and a seasonal *standard-dose* influenza vaccine versus the administration of a seasonal quadrivalent *standard-dose* influenza vaccine alone, 28 days after the administration of a seasonal influenza vaccine.

  AND

- NI of the concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone, 28 days after the administration of Ad26.COV2.S vaccine, in terms of humoral immune response (ELISA)

Therefore, the following confidence intervals (CIs) will be calculated:

- The 2-sided 95% CIs for the difference in log-transformed HI antibody titers against each of the 4 seasonal influenza vaccine strains at 28 days after the administration of the quadrivalent seasonal influenza vaccine between the Control and the CoAd group, and
- The 2-sided 95% CIs for the difference in log-transformed ELISA titers at 28 days after the administration of Ad26.COV2.S vaccine between the Control and the CoAd group

Only if the upper bound of the 2-sided 95% CI for the GMT ratio (Control group/CoAd group) of the HI antibody titer for each of the 4 vaccine strains and for S-ELISA lies below 1.5, NI of coadministration versus separate administration will be concluded for both vaccines (seasonal

influenza vaccine and Ad26.COV2.S vaccine). If 1 or more confidence limits for the GMT ratio exceed 1.5, NI cannot be concluded.

The primary analysis will be performed when all participants have completed the 28 days after the second study vaccination visit or discontinued earlier. No interim analyses will be performed.

3. SAMPLE SIZE DETERMINATION

Sample size calculations are performed under the following assumptions:

- no effect of coadministration of Ad26.COV2.S vaccine and seasonal influenza vaccine on the immune response against influenza as measured by HI antibody titers against the 4 influenza vaccine strains at 28 days after the administration of seasonal influenza vaccine
- the use of Afluria Quadrivalent for *standard-dose* (adults ≥18 to <64 years of age and older adults ≥65 years of age)
- a standard deviation of between 0.53 for the *standard-dose* at the $\log_{10}$ scale for HI antibody titers against the 4 influenza vaccine strains at 28 days after the administration of seasonal influenza vaccine (with or without Ad26.COV2.S)
- no effect of coadministration of Ad26.COV2.S vaccine and seasonal influenza vaccine on the immune response against SARS-COV-2 as measured by S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine
- a standard deviation of 0.50 at the $\log_{10}$ scale for S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine (with or without seasonal influenza vaccine)
- Log transformed (log10 scale) immune response data are normally distributed
- a non-inferiority margin of 1.5
- 2-sided α of 5%

A total of approximately 305 (*standard-dose*) participants per group are needed to have 97.45% power to show non-inferiority in HI antibody titers for each influenza vaccine strain.

The sample size accounts for exclusions from the per protocol set, drop-outs and missing samples resulting in a total sample size up to approximately 610 participants who have completed a primary COVID-19 vaccine series. The N margin was ~10% (~30 per group).

With this sample size, the overall power to show NI in HI antibody titers against each of the 4 influenza vaccine strains at 28 days after the administration of seasonal influenza vaccine as well as NI in S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine is at least 90%.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
All screened participants (ALL)	The "all screened participants" set includes all participants that were screened, regardless of whether they were enrolled and/or randomized.

Analysis Sets	**Description**
All randomized participants (ALL RANDOMIZED)	The "all randomized participants" set includes all participants that were randomized to one of the treatment groups.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all participants with a vaccine administration documented.
Per-protocol Influenza Immunogenicity (PPII) Set	Per Protocol Influenza Immunogenicity (PPII) Set: All randomized participants who received Ad26.COV2.S vaccine in combination with a seasonal influenza vaccine for the coadministration group and those who received a seasonal influenza vaccine alone for the control group, for whom immunogenicity data are available for at least one of the influenza strains in the vaccine. PPII set will include participants who have received a complete primary vaccination with an authorized/licensed COVID-19 vaccine as well as COVID-19 vaccine-naïve participants. Samples taken after (but not before) a participant experienced a confirmed major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPII analysis. The primary analysis set for analyses related to influenza immunogenicity is the PPII Set. As a sensitivity analysis, key tables may also be based on the FAS.
Per-Protocol SARS-CoV-2 Immunogenicity (PPSI) Set	The per protocol SARS-CoV-2 Immunogenicity Set (PPSI) will include all randomized participants who received Ad26.COV2.S vaccine in combination with seasonal influenza vaccine for the co-administration group and Ad26.COV2.S vaccine alone for the control group, and for whom immunogenicity data are available. PPSI set will be restricted to participants who have received a complete primary vaccination with an authorized/licensed COVID-19 vaccine. N seronegative participants at day 1 that became N serology positive during the study will be excluded for analyses of future timepoints. Participants with positive molecular test for SARS-CoV-2 will also be excluded from future timepoints. Samples taken after a participant meets the criteria for a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPSI analysis.

Analysis Sets	Description
	The primary analysis set for analyses related to SARS-CoV-2 immunogenicity is the PPSI Set. As a sensitivity analysis, key tables may also be presented as part of the FAS.
Per-Protocol SARS-CoV-2 Immunogenicity (PPSI2) Set including vaccine-naïve participants.	The per protocol SARS-CoV-2 Immunogenicity Set (PPSI2) will include all randomized participants (vaccine-naïve and previously vaccinated) who received Ad26.COV2.S vaccine in combination with seasonal influenza vaccine for the co-administration group and Ad26.COV2.S vaccine alone for the control group, and for whom immunogenicity data are available. N seronegative participants at day 1 that became N serology positive during the study will be excluded for analyses of future timepoints. Participants with positive molecular test for SARS-CoV-2 will also be excluded from future timepoints. Samples taken after a participant meets the criteria for a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPSI2 analysis.
Safety	All safety and participant information analyses will be based on the FAS.

Note: Participants who have a self-confirmed history of SARS-CoV-2 infection at screening or positive N-serology at Day 1 will be included in the analysis.

5. STATISTICAL ANALYSES

5.1. General Considerations

The primary analysis will be performed when all participants have completed the 28 days after the second study vaccination visit or discontinued earlier. No interim analyses will be performed.

5.1.1. Visit Windows

For the immunogenicity analysis, assessments will be allocated to an analysis visit based on the planned visit as captured in the CRF. Visits that are out of the protocol-defined visit windows (see Table 2) will not be included in the per-protocol immunogenicity analysis. However, they may be included in sensitivity analyses.

Table 2– Visit Windows for Immunogenicity Analysis

Analysis time point label (relative to Day 1)	Scheduled Visit Number	Visit Type	Window of target day* (Day)
[Day 1]	[2]	Vaccination 1, Immunogenicity and Safety	[N/A]
[Day 29]	[3]	Vaccination 2, Immunogenicity and Safety	[+10/-3]
[Day 57]	[4]	Immunogenicity and Safety	[+10/-3]
[Week 28]	[5]	Immunogenicity and Safety	[+7/-7]

*Relative to Analysis time point

Time windows may be redefined prior to unblinding if the number of samples excluded as per the definitions above are too numerous.

5.1.2. Study phases

The phases in the study will be considered as follows:

Phase	# Phase	Period	# Period	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post-dose period
Post-dose	2	Post-dose 1	1	Date and time of the first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b)23:59 at the database cut-off date for analyses conducted before the final analysis c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d)One second prior to post-dose 2. If a participant discontinued from the second vaccination, then the maximum of (28 days after the first vaccination at 23:59, scheduled visit 28 days after

					first vaccination at 23:59) will be used
Follow-up 1	3			One minute after Post dose 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date in case of interim analysis c) One minute prior to post dose 2
Post-dose	2	Post-dose 2	2	Date and time of the second vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 of day of second vaccination + 28 days
Follow Up 2	4			One minute after Post-dose 2 period end.	Minimum of: a) 23:59 at the date of last contact (for early discontinuation or participants that completed the study) b) 23:59 at the database cut-off date for analyses conducted before the final analysis

5.2. Participant Dispositions

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

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized

- Participants in the FAS
- Participants in the PPII
- Participants in the PPSI
- Participants who discontinued study
- Participants per SARS -CoV-2 vaccination history
- Naïve participants
- Reasons for termination of study
- Previously infected participants (in FAS, PPII and PPSI)

Listings of participants will be provided for the following categories:

- Participants vaccinated and not randomized
- Participants randomized and not vaccinated

5.3. Primary Immunogenicity Endpoints Analysis

5.3.1. Definition of Endpoints

The primary endpoints are:

- HI titers against each of the 4 influenza vaccine strains at 28 days after the administration of a seasonal quadrivalent *standard-dose* influenza vaccine.

- Antibody GMC by S-ELISA, 28 days after the administration of Ad26.COV2.S vaccine, in the *standard-dose* influenza vaccine groups.

The HAI analysis is based on vaccine specific strains, therefore, for the NI assessment that concerns the *standard dose* of the flu vaccine. The following vaccine-specific strains will be used:

A/Victoria (H1N1)
A/Cambodia (H3N2)
B/Victoria (B/Victoria)
B/Phuket (B/Yamagata)

5.3.2. Analysis Methods

The NI immunogenicity objectives will be assessed in PPII and PPSI analysis sets by calculating:

- the 2-sided 95% CIs for the difference in log-transformed HI antibody titers against each of the 4 influenza vaccine strains at 28 days after the administration of the seasonal influenza vaccine between the Control and the CoAd group for the standard-dose.

- the 2-sided 95% CIs for the difference in log-transformed S-ELISA titers at 28 days after the administration of Ad26.COV2.S vaccine between the Control and the CoAd group.

For *HI antibody titers* against each of the 4 influenza vaccine strains and for *S-ELISA titers*, an analysis of variance (ANOVA) model will be fitted with the respective titers as dependent variable and group (Control or CoAd), age category (as stratified), previous SARS-CoV-2 vaccination (as collected), and baseline S-ELISA titers as independent variable. The strata will be based on the values in the database for vaccination history (which may differ to the strata as recorded in IWRS).

Based on these ANOVA models, the CIs around the difference will be calculated and will be back transformed (by exponentiation) to CIs around a GMC or GMT ratio (Control group / CoAd group), respectively, and compared to the NI margin of 1.5.

Only if the upper bound of the 2-sided 95% CI for the GMT or GMC ratio (Control group/CoAd group), respectively, of the HI antibody titer for each of the 4 vaccine strains and for S-ELISA lies below 1.5, NI of coadministration versus separate administration will be concluded for both vaccines (seasonal influenza vaccine and Ad26.COV2.S vaccine). If 1 or more confidence limits for the GMC or GMT ratio exceed 1.5 non-inferiority cannot be concluded.

For immunogenicity, baseline is considered as the last assessment pre-vaccination (i.e. it corresponds to Day 1 for CoAd groups or influenza vaccine alone, or to Day 29 for Control groups or Ad26.COV2.S vaccine alone). In a sensitivity analysis, different variances between the groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

The assessment of the primary endpoints will be performed on individuals who have been previously vaccinated with different types of COVID-19 vaccines. Furthermore, participants may have or not an history of COVID infection. These factors bring a level of variability of immune responses that is unknown.

The populations for analyses related to influenza immunogenicity and COVID-19 immunogenicity are the PPII set and the PPSI set, respectively. The choice of population for the different analyses are described in Section 4.

Descriptive statistics

To describe the humoral immune response in groups at Day 29 following each vaccination, the following statistics will be calculated for HI antibody titers and S-ELISA titers: N, geometric mean and corresponding 95% CI of the actual values (see below), fold increase from baseline, number of positive samples (definition see below), the number of responders (definition see below). seroprotection, seroconversion.

Geometric mean and 95% CI

For the calculation of the geometric mean and its 95% confidence interval (CI), we assume that the $\log_2$ and $\log_{10}$ transformed values of HI antibody and S-ELISA concentrations respectively are normally distributed. Therefore, the calculation of the geometric mean and the corresponding 95%

CI will be done in the following way: (1) the arithmetic mean and its corresponding 95% CI (using the t-distribution) are calculated on the $\log_2$ and $\log_{10}$ transformed values of concentration; (2) these values are back transformed to provide the geometric mean and its corresponding 95% CI concentration.

Positive Sample

A sample will be considered positive if the value is strictly greater than the LLOQ (>LLOQ).

Responder

A post-baseline sample will be considered a responder if at least one of the following conditions is satisfied:

- The baseline sample value is less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample is strictly greater than the LLOQ (>LLOQ)
- The baseline sample value is strictly greater than the LLOQ (>LLOQ) and the post-baseline sample value represents an at least 4-fold (≥4-fold) increase from the baseline sample value.

Seroconversion

defined for each of the 4 influenza vaccine strains at 28 days after the administration of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine:

- HI titer ≥1:40 in participants with a pre-vaccination HI titer of <1:10, or
- a ≥4-fold HI titer increase in participants with a pre-vaccination HI titer of ≥1:10.

Seroprotection

defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 28 days after the administration of a seasonal quadrivalent (*high-dose* and *standard-dose*) influenza vaccine.

5.3.3. 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) will be imputed based on the type of analysis:

- Values below LLOQ will be imputed to LLOQ/2, except for the calculation of the geometric mean of the increase from baseline where values below LLOQ will be imputed to LLOQ.

- Values above the upper limit of quantification (ULOQ) or Max Range will be imputed with the ULOQ / Max Range.

The ULOQ / Max Range and LLOQ values per assay will be available in the database.

5.4. Secondary Endpoints Analysis

5.4.1. Secondary Immunogenicity Endpoints

5.4.1.1. Definition of Endpoints

The secondary immunogenicity endpoints are:

- If a participant has positive N serology, then the individual is considered seropositive.

When including vaccine naive individuals in the analysis, if the individual has detectable S Elisa titers above the limit of quantification and/or positive N serology, then the individual is considered seropositive.The confirmation of serostatus will be performed with a sensitive S-ELISA and/or N serology assay.

- Previous history of vaccination defined as previously vaccinated individuals (ie, Vaxzevria [AstraZeneca], Comirnaty [Pfizer-BioNTech], SpikeVax [Moderna], and Ad26.COV2-S [Janssen]), regardless of previous SARS-CoV2 infection.

The following will be presented descriptively for the secondary analyses:

- Humoral immune response as measured by the HI assay after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of a seasonal quadrivalent *standard-dose* influenza vaccine alone, 28 days after the administration of a seasonal influenza vaccine.

- Humoral immune response (ELISA) following concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone, 28 days after the administration of Ad26.COV2.S vaccine.

- Humoral immune response as measured by the HI assay after concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine versus the administration of a seasonal quadrivalent *high-dose* influenza vaccine alone, 28 days after the administration of a seasonal influenza vaccine.

- Humoral immune response (ELISA) following concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine

versus the administration of Ad26.COV2.S vaccine alone, 28 days after the administration of Ad26.COV2.S vaccine.

For COVID-19 vaccine-naïve individuals, the following will be presented:

- Humoral immune response (ELISA) following concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *high-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone, 28 days after the administration of Ad26.COV2.S vaccine in COVID-19 vaccine-naïve individuals.
- Humoral immune response (ELISA) following concomitant administration of Ad26.COV2.S vaccine and a seasonal quadrivalent *standard-dose* influenza vaccine versus the administration of Ad26.COV2.S vaccine alone, 28 days after the administration of Ad26.COV2.S vaccine in COVID-19 vaccine-naïve individuals.

The HAI analysis is based on vaccine specific strains, therefore, for the *high dose* of the flu vaccine (descriptive analysis) the following vaccine-specific strains will be used:

A/Victoria (H1N1)
A/Tasmania (H3N2)
B/Washington (B/Victoria)
B/Phuket (B/Yamagata)

5.4.1.2. Analysis Methods

To assess the humoral immune response to SARS-CoV-2 in vaccination groups, the following statistics will be calculated for the different assays for each vaccination group at each time point: N, geometric mean and corresponding 95% CI of the actual values, fold increase from baseline, number of positive samples, the number of responders (see Section 5.3.2).

To compare seroconversion and seroprotection rates against the 4 influenza vaccine strains, the proportion of seroconverted and seroprotected participants will be tabulated. The difference in proportions of seroconverted and seroprotected participants between the Control and the CoAd group will be estimated together with the 2-sided 95% CIs (calculated using Wilson's score method).

Additionally, HI antibody titers and S-ELISA titers will be summarized with descriptive statistics. Descriptive statistics (geometric mean and 97.5% CI) of the actual values will be calculated for continuous immunogenicity parameters at all timepoints. Geometric mean fold increases from baseline and corresponding 95% CIs might additionally be calculated. Graphical representations of immunogenicity parameters will be created as applicable.

For categorical variables, frequency tables will be presented. Difference in proportions and corresponding CIs may be calculated where appropriate.

Actual values and fold changes from baseline will also be presented in dot-plots with dots for participant values, and the corresponding geometric mean and 95% CI per timepoint for each assay. In addition, plots of GMT over time, combining the regimens in one graph (without individual participant dots) will be created. Participant profiles of the actual values over time will be graphically presented. Reverse distribution curves of the actual values will be provided for selected timepoints. In the graphs, original values will be displayed on the $\log_2$ or $\log_{10}$ scale.

Refer to Section 5.3.3 for instructions on how immune response values below LLOQ, values above ULOQ / Max Range and missing values will be handled.

5.4.2. Secondary Safety Endpoints

See Section 5.6.

5.5. Exploratory Endpoints Analysis

5.5.1. Definition of Endpoints

The exploratory endpoints are:

- GMT: Geometric mean of HI antibodies and percentages of participants with HI titers ≥1:40, *at Day 181*.
- Antibody GMC by S-ELISA *at Day 181* after the administration of Ad26.COV2.S vaccine.
- Serological responses *magnitude and durability at Day 181* to vaccination as measured by ELISA at Day 181 after the administration of influenza vaccine.
- Serological response to vaccination, as measured by virus neutralization assay (VNA) (SARS-CoV-2 VNA and/or pseudo virion [ps] VNA expressing S protein) titers, in a subset of participants.
- Adenovirus 26 neutralization responses measured by VNA.
- Functional and molecular antibody characterization including Fc-mediated viral clearance, avidity, Fc characteristics, immunoglobulin (Ig) subclass, and IgG isotype.
- Humoral responses to Ad26.COV2.S and influenza vaccine based on the SARS-CoV-2 serostatus at baseline (N-serology).
    - Serological response to vaccination as measured by S-ELISA antibody concentration 28 days after the administration of Ad26.COV2.S vaccine
    - Antibody GMC by S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine.
    - Antibody HI titers as measured by HAI assay titers (GMTs) against the 4 influenza strains.
- Humoral responses to Ad26.COV2.S and influenza vaccine based on the previous history of COVID-19 vaccination at entry (viral vector vaccine or mRNA vaccine or vaccine-naïve)
    - Serological response to vaccination as measured by S-ELISA antibody concentration 28 days after the administration of Ad26.COV2.S vaccine.
    - Antibody GMC by S-ELISA at 28 days after the administration of Ad26.COV2.S vaccine.

- Antibody HI titers as measured by HAI assay titers (GMTs) against the 4 influenza strains.

5.5.2. Analysis Methods

For humoral or serological response to vaccination method, *at Days 1, 29, 57 and 181 ,* and for *durability at Week 28* or *as measured by virus neutralization assay (VNA)*, or *based on history of vaccination at entry* (it could be: Vaxzevria [AstraZeneca], Comirnaty [Pfizer-BioNTech], SpikeVax [Moderna], and Ad26.COV2-S [Janssen] or naïve), the methods are similar to those used for humoral immune response for primary and secondary endpoints (see Section 5.3.2 and 5.4.1.2).

Adenovirus 26 neutralization will be measured in all subjects at baseline to assess the seroprevalence of Ad26 and to assess immunogenicity against the vector. Descriptive statistics (N, geometric mean and corresponding 95% CI, number and percentage of positive samples) will be calculated.

In case there is a significant number of seropositive participants, Spearman correlation between Ad26 neutralizing antibody concentrations and S-ELISA concentrations in the combined regimens will be calculated and will be visualized with a scatter plot.

SARS-CoV-2 neutralizing titers in serum measured by VNA i.e. (wild-type virus and/or pseudovirion[ps] expressing S protein) at all selected timepoints i.e. Day 1 (pre-vaccination) i.e. Baseline, Day 29, Day 57 and Week 24 (and in case of early exit at the exit visit), for a subset of the participants.

The correlation between the binding antibody (S-ELISA) concentrations and neutralizing antibody (VNA) titers to SARS-CoV-2 will be assessed at the different timepoints in a subset of participants using Spearman's rank correlation. A scatterplot between S-ELISA and VNA will be provided at the different time points.

5.6. Safety Analyses

The Safety and reactogenicity endpoints (secondary endpoints) are:

- Solicited local (injection site) and systemic AEs for 7 days after each vaccination
- Unsolicited AEs for 28 days after each vaccination
- SAEs, MAAEs, and AESIs throughout the study.
- AEs leading to withdrawal from the study throughout the study.

These endpoints will be assessed in both participants aged *65 years and older*, and participants aged *18 years and older.*

5.6.1. Adverse Events

5.6.1.1. Definitions of Adverse Events Endpoints

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF. For unsolicited AEs, only the AEs within the 28-day period following each vaccination will be presented in the safety tables except for SAE, MAAEs and AESI cases which will be captured and tabulated in the outputs covering the whole study period.

Local solicited AEs symptoms will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as toxicity grade 1 to 4 (refer to appendix 7). Solicited events of grade 0, not reported in the CE domain, will therefore not be reported in the AE analysis.

5.6.1.2. Analysis of Adverse Events

Safety analyses will be performed on the FAS. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, median, minimum, and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

Safety data will be analyzed and presented by study intervention and phase. Denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

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), time to onset (in days) and duration (in days). 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 date is the start date of the vaccination period.

A tabulation of the distribution of temperatures per half degree intervals will also be provided.

For unsolicited AEs, the following tables will be provided: summary table (including SAE, fatal outcome, discontinuation and AESI), all events, most frequent, at least grade 3, permanent stop of vaccine, related, SAE, related SAE, potential AESI and AESI.

Unsolicited non-serious adverse events collected outside the 28-day period following the vaccination will be presented through listings.

Listings and/or participant narratives will be provided as appropriate, for those participants with a fatal outcome, discontinue study vaccinations due to an AE, discontinue study due to an AE, or experienced a severe SAE, or an AESI event.

5.6.1.3. Phase Allocation of Adverse Events

For this study, 3 phases are defined: screening, treatment and follow-up.

As the analysis of solicited events will be based on the overall assessment of the investigator which is documented in the CE domain, the Analysis Data Model (ADaM) dataset will be based on the CE domain. Solicited events are allocated to the phases as described below, however they are always allocated to the respective post-dose period and will never be attributed to the screening phase. Time of day is not considered while attributing solicited AEs to phases.

For unsolicited AEs, the steps below are followed as well.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM (Study Data Tabulation Model) database 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. The imputed end dates will not be shown in the data listings. In case of a completely missing start date, the event is allocated to the first active phase (post dose 1 period), except if the end date of the AE falls before the start of the first active 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 phases/periods - Screening or Follow-up (defined as non-active periods) - followed by an AE in - Post-dose period (defined as active period) - they are allocated to their respective phases/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 database 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 consecutive 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 database but are assigned the same onset, treatment 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. In case overlapping/consecutive events start in non-consecutive periods (regardless of active or non-active), they are allocated to their respective period and are considered as separate AEs.

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.

5.6.1.4. Missing Adverse Event Data

Missing data will not be imputed. Participants who do not report an event will be considered as participants without an event. 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. The analysis of solicited AEs will include the safety data as documented by the investigator.

5.6.1.5. COVID-19 case

At each visit the participant will be asked if they have had a private/off-study COVID-19 test. If a participant receives a positive SARS-CoV-2 result from a private/off-study test during the study, and the positive result occurs within 28 days after vaccination, the event will be reported as an AE. If it occurs after 28 days, the event will be recorded as an SAE only if the event qualifies as serious. If the event occurs after 28 days, and it is not serious, it will not be reported in the eCRF.

Any positive SARS-CoV- 2 result should be recorded in the eCRF.

A listing with all COVID cases throughout the study will be created including the severity, the onset, the duration and any other relevant information for the event will be created.

5.6.2. Other Safety Analyses

5.6.2.1. Clinical Laboratory Tests

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

Local lab results reported without units/ranges are not evaluable for grading and severity. Such events will be displayed in a separate listing.

5.6.2.2. Vital Signs and Physical Examination Findings

Baseline and emerging vital signs abnormalities after vaccination will be listed based on the abnormality gradings in Appendix 7 (Section 6.7). An abnormality 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.

5.7. Other Analyses

5.7.1. Subgroup Analysis

For exploratory purpose, subgroup analyses for the primary endpoints (and vaccine-naïve participants) related to humoral response will be done (but are not limited) for the following subgroups if significant balance is achieved:

5.7.1.1. Age

This exploratory analysis intents to assess the effect of Age, regarding the humoral response.

Subgroup	**Definition**
Age Group	• >=18 to <=64 years • >=65 years

5.7.1.2. Humoral responses to Ad26.COV2.S based on the SARS-CoV-2 serostatus at baseline (N-serology) and the previous history of COVID-19 vaccination at entry

This exploratory analysis intents to assess the effect of previous infection or not by natural SARS-CoV-2.

Subgroup	**Definition**
Previously natural SARS-CoV-2 infected participants	• Previously infected • Not previously infected

No specific actions are made to balance previously infected participants. The analysis will be conducted as exploratory purpose.

Subgroup	**Definition**
Participants receiving primary series vaccine at entry	• Vaxzevria [AstraZeneca] • Comirnaty [Pfizer-BioNTech] • SpikeVax [Moderna] • Ad26.COV2-S [Janssen] Or • mRNA • Adeno based

The combination of these 2 factors will be assessed if the groups numbers are deemed relevant.

5.7.1.3. Humoral responses to influenza vaccine based on the SARS-CoV-2 serostatus at baseline (N-serology) and the previous history of COVID-19 vaccination at entry

This exploratory analysis intents to assess the effect of primary series vaccine at study entry (Vaxzevria [AstraZeneca], Comirnaty [Pfizer-BioNTech], SpikeVax [Moderna], and Ad26.COV2-S [Janssen]) and serostatus at baseline. The combination of these 2 factors will be assessed if the groups numbers are deemed relevant.

HI analysis will be conducted as an exploratory endpoint to evaluate immune response elicited by the co-administered influenza based on COVID-19 vaccine serostatus and pre-vaccination history.

The serological response to vaccination will be measured by HI titers against each of the 4 influenza vaccine strains at 28 days after the administration of a seasonal quadrivalent (high-dose and standard-dose) influenza vaccine. Then, the geometric mean titer of HI antibodies at 28 days after the administration of a seasonal quadrivalent (high-dose and standard-dose) influenza vaccine will be described for each subgroup.

5.7.2. Primary and Final Analysis

The primary analysis of safety and immunogenicity will be performed when all participants have completed the 28 days after the second study vaccination visit or discontinued earlier. The primary

analysis will be performed based on sponsor's unblinded data (sponsor, study-site personnel and participants will remain blinded during the treatment phase up to the database lock).

A final analysis will be performed when all participants have completed the 6 months follow-up period after the second vaccination or discontinued earlier.

5.8. Data Monitoring Committee (DMC)

No Data Monitoring Committee (DMC) has been planned for this study.

5.9. Interim Analyses

No interim analyses will be performed.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

Ad26	adenovirus serotype 26
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse events of special interest
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
COVID-19	COVID-19 coronavirus disease-2019
CRF	case report form
CSR	Clinical Study Report
CTP	clinical trial protocol
CV	coefficient of variation
DPS	Data Presentation Specifications
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
GMT	geometric mean titre
HAI	hemagglutination inhibition assay
HI	hemagglutination inhibition
ICH	International Conference on Harmonisation
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MAAE	medically attended adverse events
PI	principal investigator
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

For HI antibody titers against each of the 4 influenza vaccine strains and for S-ELISA titers, an analysis of variance (ANOVA) model will be fitted with the respective titers as dependent variable and group (Control or CoAd), age category (as stratified), previous SARS-CoV-2 vaccination (as collected), and baseline S-ELISA titers as independent variable.
The strata will be based on the values in the database for vaccination history (which may differ to the strata as recorded in IWRS).

In order to evaluate the cross-reactivity between HAs, we will analyze the HI responses to mis/unmatched vaccine strains. This analysis will be performed in a subset of participants, namely, study participants that are 65 yo and older. Samples will be tested specifically for the H3N2 and the B/Victoria influenza strains. Participants corresponding to Groups 1 and 2 will be analyzed for the following non-matched strains: A/Tasmania and B/Washington. Participants corresponding to Groups 3 and 4 will be analyzed for the following non-matched strains: A/Cambodia and B/Victoria.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by vaccination group, and overall. In addition, the distribution of participants country, and site ID will be presented unless otherwise noted.

Table 3 presents a list of the demographic variables that will be summarized by vaccination groupand overall for the FAS analysis set. Demographics will also be summarized by country using the FAS analysis set.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18-64 years, and >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2)	

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

6.4. Appendix 4 Protocol Deviations

In general, the predefined 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.

Minor and major protocol deviations related to COVID-19 will be tabulated separately.

6.5. Appendix 5 Prior and Concomitant Medications

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

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. The same rule applies for identifying whether a concomitant therapy was administered during 8 days following a vaccination. If for example, the vaccination was administered on the 30 December 2017 and the concomitant therapy start date is January 2018, then the concomitant therapy will be assumed to have started within 8 days of the vaccination.

- In case of a of a completely missing start date, the concomitant therapy will be considered as having started before the study.

- 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 that started during 8 days following each vaccination (00:00 of day of vaccination + 7 days). Following 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) (ATC/DD Index). 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.

6.6. Appendix 6 Adverse Events of Special Interest

Thrombosis with thrombocytopenia syndrome (TTS) is considered to be an AESI. Suspected AESIs (thrombotic events and thrombocytopenia (defined as platelet count below 150,000/µL [Brighton Collaboration 2021]) will be reported from the moment of vaccination until the end of the study/early withdrawal. See Appendix 10.9 of the CTP, for the definition of a suspected AESI.

An AESI Adjudication Committee with appropriate expertise will be established to evaluate each suspected AESI and determine whether it is a case of TTS (see Section 10.3.6 of the CTP).

6.7. Appendix 7 Toxicity Grading Scales

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

Tables for Clinical Abnormalities

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

[#] Revised by the sponsor.

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

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

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

[#] Revised by the sponsor.

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

[#] Revised by the sponsor.

7. REFERENCES

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