

Janssen Vaccines & Prevention B.V.

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Immunogenicity and Safety of Ad26.RSV.preF-based Vaccine and High-dose Seasonal Influenza Vaccine, With and Without Coadministration, in Adults Aged 65 Years and Older

Protocol VAC18193RSV3005; Phase 3

VAC18193 (JNJ-64400141/JNJ-64213175)

Status: Approved
Date: 5 July 2022
Prepared by: Janssen Vaccines & Prevention B.V.
Document No.: EDMS-RIM-371607, 2.0

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

Confidentiality Statement

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

TABLE OF CONTENTS

TABLE OF CONTENTS	2
VERSION HISTORY	3
1. INTRODUCTION.....	4
1.1. Objectives and Endpoints	4
1.2. Study Design	4
2. STATISTICAL HYPOTHESES	4
3. SAMPLE SIZE DETERMINATION.....	5
4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS	5
5. STATISTICAL ANALYSES	6
5.1. General Considerations	6
5.1.1. Study Phases.....	6
5.1.2. Phase Definitions	6
5.1.3. Visit Windows	8
5.2. Participant Dispositions.....	9
5.3. Primary Endpoint(s) Analysis	10
5.3.1. Definition of Endpoint(s)	10
5.3.2. Analysis Methods.....	10
5.3.3. Handling of Missing and/or Unquantifiable Immune Response Data.....	11
5.4. Secondary Endpoint(s) Analysis	11
5.4.1. Secondary Immunogenicity Endpoint(s)	11
5.4.1.1. Definition of Endpoint(s)	11
5.4.1.2. Analysis Methods	11
5.5. Safety Analyses	12
5.5.1. Adverse Events.....	12
5.5.1.1. Definitions	12
5.5.1.2. Analysis of Adverse Events	13
5.5.1.3. Phase Allocation of Adverse Events	14
5.5.1.4. Missing Data	16
5.5.2. Vital Signs.....	16
5.6. Other Analyses.....	16
5.6.1. Definition of Subgroups	16
5.7. Interim Analyses.....	16
5.7.1. Independent Data Monitoring Committee (IDMC)	16
6. SUPPORTING DOCUMENTATION	18
6.1. Appendix 1: List of Abbreviations.....	18
6.2. Appendix 2: Demographics and Baseline Characteristics	19
6.3. Appendix 3: Protocol Deviations	20
6.4. Appendix 4: Prior and Concomitant Medications	21
6.5. Appendix 5: Toxicity Grading Scale for Vital Signs.....	22
7. REFERENCES.....	23

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	28 September 2021	Not Applicable	Initial release
2.0	5 July 2022	<ul style="list-style-type: none"> • Update definition and analysis of AESIs (section 5.5.1) • Updating the Phase Definition table (Table 3) as split Day 29 visits are allowed per protocol amendment 2. • Updating the Phase Definition table for Follow-Up 1 and Follow-Up 2 for subjects who discontinued from 2nd vaccination • Updating the definitions of interval (Table 4), for 57-6m and >6m for subjects in the CoAd group • Updating Visit Windows for Immunogenicity Analysis (Table 5 and 6) • Adding a sensitivity analysis for solicited adverse events • Adding an imputation rule in case the start date-time of a given vaccination at Day 1 is missing and the start date-time of the concomitant vaccination is available. • Removal of the temperature analysis by half degree intervals. 	<ul style="list-style-type: none"> • Updates after Protocol Amendment 2 • Clarification of the analysis

1. INTRODUCTION

This statistical analysis plan (SAP) contains information needed to perform the complete safety and immunogenicity analysis of the VAC18193RSV3005 trial. It applies to all the analyses described in Section 9.5 of the clinical trial protocol (CTP). The specifications of individual tables, listings and figures to be generated in each analysis will be described in a separate data presentation specifications (DPS) document.

1.1. Objectives and Endpoints

Refer to Section 3 of the CTP. The statistical hypotheses are described in Section 2 of this document.

1.2. Study Design

Refer to Section 4.1 of the CTP for details on the study design, and section 6.3 of the CTP for details on randomization and procedures for maintaining the blind.

2. STATISTICAL HYPOTHESES

To demonstrate the non-inferiority of the concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine versus the administration of a seasonal influenza vaccine alone, 28 days after the administration of a seasonal influenza vaccine, in terms of humoral immune response as measured by the hemagglutination inhibition assay (HI assay),

AND

to demonstrate the non-inferiority of the concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine versus the administration of Ad26/protein preF RSV vaccine alone, 28 days after the administration of Ad26/protein preF RSV vaccine, in terms of humoral immune response (pre-F ELISA).

The following hypotheses will be tested:

Null Hypothesis:

- For at least 1 of the 4 influenza vaccine strains: the GMT of HI antibody titers against the considered vaccine strain, 28 days after concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine is inferior by at least 1.5 to the GMT 28 days after the administration of a seasonal influenza vaccine alone (for the ratio $GMT_{Control\ group}/GMT_{CoAd\ group}$)

OR

- The GMT of pre-F ELISA titers 28 days after concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine is inferior by at least 1.5 to the GMT 28 days after the administration of Ad26/protein preF RSV vaccine alone (for the ratio $GMT_{Control\ group}/GMT_{CoAd\ group}$)

Alternative Hypothesis:

- For each of the 4 influenza vaccine strains: the GMT of HI antibody titers 28 days after concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine is non-inferior to the GMT 28 days after the administration of a seasonal influenza vaccine alone, using a non-inferiority margin of 1.5, for the ratio $GMT_{Control\ group}/GMT_{CoAd\ group}$

AND

- The GMT of the pre-F ELISA titers 28 days after concomitant administration of Ad26/protein preF RSV vaccine and a seasonal influenza vaccine is non-inferior to the GMT 28 days after the administration of Ad26/protein preF RSV vaccine alone, using a non-inferiority margin of 1.5, for the ratio $GMT_{Control\ group}/GMT_{CoAd\ group}$

3. SAMPLE SIZE DETERMINATION

Refer to Section 9.2 of the CTP.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For vaccine studies, study intervention assignment will follow the as treated principle. The definition of the analysis is given in [Table 2](#).

Table 2: Description of Analysis Sets

Analysis Sets	Description
All Screened	<p>This analysis set includes all participants screened for the study, regardless if they were screen failures or they got enrolled in the study.</p> <p>Rescreened participants are counted only once.</p>
Full Analysis Set (FAS)	<p>The full analysis set (FAS) will include all participants who received at least 1 study vaccination, regardless of the occurrence of protocol deviations and vaccine type (seasonal influenza, Ad26/protein preF RSV vaccine, or placebo).</p> <p>All safety and participant information analyses will be based on the FAS.</p>
Per-protocol Influenza Immunogenicity (PPII) Set	<p>The Per-protocol Influenza Immunogenicity (PPII) Set will include all randomized participants who received the first study vaccination, and for whom immunogenicity data are available for at least one of the influenza strains in the vaccine. Samples taken after a participant experienced a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPII analysis*.</p> <p>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.</p>
Per-protocol RSV Immunogenicity (PPRI) Set	<p>The Per-protocol RSV Immunogenicity (PPRI) Set will include all randomized participants who received Ad26/protein preF RSV vaccine in combination with</p>

Table 2: Description of Analysis Sets

Analysis Sets	Description
	<p>seasonal influenza vaccine for the CoAd group and Ad26/protein preF RSV vaccine alone for the Control group and for whom RSV immunogenicity data are available. Samples taken after a participant experienced a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPRI analysis*.</p> <p>The primary analysis set for analyses related to RSV immunogenicity is the PPRI Set. As a sensitivity analysis, key tables may also be based on the FAS.</p>

* The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the major protocol violation criteria document, which will be finalized before database lock and unblinding.

Note: If a subject received at Day 1 both vaccinations but the start date-time of one of the vaccination is not available in the clinical database, this date-time will be imputed with the date-time of the other vaccination.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Study Phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the vaccination on Day 1. Except the baseline value of the control group (Group 2) for the immunogenicity endpoints related to RSV, which will be the value of the last available assessment prior to the second vaccination (Ad26/protein preF RSV vaccine) (i.e. Day 1 for post-dose 2).

If there was no immunogenicity assessment done pre-vaccination, the assessment post-vaccination on Day 1 (or on the day of the 2nd vaccination for RSV immuno titers in the control group) can be used as the baseline value for the immunogenicity analysis, if available.

The results of the safety analysis will be presented by phase. Immunogenicity results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

Study day or relative day is defined as follows:

- Study Day = visit date – date of Day 1* + 1; if visit date \geq 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).

*For immunogenicity endpoints related to RSV in post-dose 2 of the control group, the day of second vaccination will be considered as Day 1.

5.1.2. Phase Definitions

The phases in the study will be constructed as follows:

Table 3: Phase Definitions

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 1 period
Regimen	2	Post-dose 1	1	Date and time of first vaccination	<p>Minimum of:</p> <ul style="list-style-type: none"> 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) 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 d) For subjects with no split Day 29 visit (i.e. scheduled Day 29 visit = day of 2nd dose): One minute prior to post-dose 2. e) For subjects with a split Day 29 visit (i.e. scheduled day 29 visit < day of 2nd dose): scheduled visit 28 days after first vaccination at 23:59)
Follow-up 1	3			<p>Only for subjects with a split Day 29 visit or subjects who discontinued from 2nd vaccination:</p> <p>One minute after Post-dose 1 period end</p>	<p>Only for subjects with a split Day 29 visit:</p> <p>One minute prior to post-dose 2</p> <p>For subjects who discontinued from the 2nd vaccination:</p> <p>Minimum of:</p> <ul style="list-style-type: none"> 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
Regimen	2	Post-dose 2	2	Date and time of second vaccination	<p>Minimum of:</p> <ul style="list-style-type: none"> 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) maximum of (28 days after the 2nd vaccination at 23:59, scheduled visit 28 days after 2nd vaccination at 23:59)
Follow-up-2	4			One minute after Post-dose 2 period end.	<p>Minimum of:</p> <ul style="list-style-type: none"> 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

The adverse events of special interest (AESI) analysis will be performed once by phase and once by time interval. The definition of the time intervals is shown in the [Table 4](#) below. Additionally, in the tables a ‘0-56 days post-dose’ interval and a ‘0-6 months post-dose’ interval should also be shown. The ‘0-56 days post-dose’ interval is the combination of the ‘0 - 28 days post-dose’ interval and the ‘29 - 56 days post-dose’ interval. The ‘0-6 months post-dose’ interval is the combination of the ‘0 - 28 days post-dose’, ‘29 - 56 days post-dose’ and ‘57 days - 6 months post-dose’ intervals. Note that the ‘>6 months’ time-interval will only be included in listings.

Table 4: Definition of intervals

Dose	Interval	From	to
Post RSV vaccination	0 - 28 days post dose	Date time of the RSV vaccination	<ul style="list-style-type: none"> For subjects in the Coad group (group 1): end of the post-dose 1 period For subjects in the Control group (group 2): end of the post-dose 2 period
	29 - 56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: <ul style="list-style-type: none"> 23:59 at date of last contact (for discontinuations) 23:59 at date of DB cut-off for interim analyses Date of RSV Vaccination + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29 - 56 days post dose	Min of: <ul style="list-style-type: none"> 23:59 at date of last contact (for discontinuations/completions) 23:59 at date of DB cut-off for interim analyses For subjects in the Coad group (group 1): Date of RSV Vaccination + 183 days at 23:59
	For Coad group only: >6 months post-dose	One minute after the end of the interval 57 days – 6 months post dose	Min of: <ul style="list-style-type: none"> 23:59 at date of last contact (for discontinuations/completions) 23:59 at date of DB cut-off for interim analyses

5.1.3. 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 5](#) and [Table 6](#) below) will not be included in the per-protocol immunogenicity analysis. However, they may be included in sensitivity analyses.

Table 5: Visit Windows for pre-F ELISA titers Analysis

Analysis time point label (Relative to Ad26. RSV vaccination)		Corresponding CTP Visit Day	Reference day	Target day (from reference day)	Window of target day (days)
CoAdmin Group	Day 1	Day 1	Day of vaccination 1	1	(-∞, 1]
	Day 29	Day 29	Day of vaccination 1	29	[24, 34]
	Day 57	Day 57	Day of vaccination 2	29	[22, 36]
Control Group	Day 1	Day 29	Day of vaccination 2	1	(-∞, 1]
	Day 29	Day 57	Day of vaccination 2	29	[22, 36]

Table 6: Visit Windows for HI antibody titers Analysis

Analysis time point label (Relative to FLU. vaccination)		Corresponding CTP Visit Day	Reference day	Target day (from reference day)	Window of target day (days)
Day 1	Day 1	Day 1	Day of vaccination 1	1	(-∞, 1]
Day 29	Day 29	Day 29	Day of vaccination 1	29	[24, 34]
Day 57	Day 57	Day 57	Day of vaccination 2	29	[22, 36]

5.2. Participant Dispositions

Participant information will be shown for the full analysis set.

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

- participants screened
- participants in the FAS
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants not randomized and not vaccinated
- participants randomized and vaccinated
- participants who discontinued study
- participants who discontinued vaccination
- reasons for termination

Also, the number of participants and percentage per phase will be tabulated.

Other participant information variables: demographics and baseline characteristics, major protocol deviations, and concomitant medications will be analyzed as described in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#), respectively. Medical history and concomitant diseases will be tabulated.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary endpoints are:

- HI titers against each of the 4 influenza vaccine strains at 28 days after the administration of a quadrivalent high-dose seasonal influenza vaccine.
- Pre-F ELISA antibody titers at 28 days after the administration of Ad26.RSV.preF-based vaccine.

5.3.2. Analysis Methods

The primary immunogenicity objectives will be assessed by calculating:

- the 2-sided 95% CIs for the difference in \log_2 -transformed HI antibody titers against each of the 4 influenza vaccine strains at 28 days after the administration of the quadrivalent high-dose seasonal influenza vaccine between the Control and the CoAd group.
- the 2-sided 95% CIs for the difference in \log_2 -transformed pre-F ELISA titers at 28 days after the administration of Ad26/protein preF RSV vaccine between the Control and the CoAd group.

For HI antibody titers against each of the 4 influenza vaccine strains and for pre-F ELISA titers, an analysis of variance (ANOVA) model will be fitted (using SAS proc mixed) with the respective titers as dependent variable, and group (Control or CoAd) and age category (as stratified) as independent variable. Based on these ANOVA models, the CIs around the difference will be calculated and will be back-transformed to CIs around a GMT ratio ($GMT_{Control\ group}/GMT_{CoAd\ group}$) and compared to the non-inferiority margin of 1.5.

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 pre-F ELISA lies below 1.5, non-inferiority of coadministration versus separate administration will be concluded for both vaccines (seasonal influenza vaccine and Ad26/protein preF RSV vaccine). If 1 or more confidence limits for the GMT ratio exceed 1.5, non-inferiority cannot be concluded.

As a sensitivity analysis to assess the impact of baseline titers, the primary endpoint will also be evaluated adjusting for the respective baseline titers. In a second sensitivity analysis, different variances between the groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA using SAS proc mixed with a repeated statement (repeated / group=).

The significance level (α) is 5% (2-sided). As both non-inferiority objectives should be demonstrated to have a successful study and as no interim analyses before the primary analysis are planned, no multiplicity adjustments are needed.

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

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) will be imputed with the ULOQ.

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

5.4. Secondary Endpoint(s) Analysis

5.4.1. Secondary Immunogenicity Endpoint(s)

5.4.1.1. Definition of Endpoint(s)

- Seroconversion is defined for each of the 4 influenza vaccine strains at 28 days after the administration of a quadrivalent high-dose seasonal influenza vaccine:
 - HI titer $\geq 1:40$ 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 $\geq 1:10$
- Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer $\geq 1:40$ at 28 days after the administration of a quadrivalent high-dose seasonal influenza vaccine

5.4.1.2. Analysis Methods

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 pre-F ELISA titers will be summarized with descriptive statistics. Descriptive statistics (N, geometric mean[§] and corresponding 95% 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.
§ calculate the mean and corresponding 95%CI of the log₂-transformed values, back-transform this mean [i.e. 2^mean] and CI [i.e. 2^CI].

The tables will also show the fold increases from baseline together with the percentage of participants with an x-fold increase from baseline (for several values of x).

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 log₂ scale.

Refer to Section [5.3.3](#) for instructions on how immune response values below LLOQ, values above ULOQ and missing values will be handled.

5.5. Safety Analyses

Safety endpoints (secondary endpoints):

- Solicited local (injection site) and systemic AEs for 7 days after each vaccination
- Unsolicited AEs for 28 days after each vaccination
- Serious adverse events (SAEs) and adverse events of special interest (AESIs) until 6 months after the second study vaccination until 6 months after the second study vaccination

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 analysed and presented by study intervention and phase, and also across the entire study period where applicable. For unsolicited AE, the denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase). For solicited AEs, the denominator for the percentages is the number of participants with data assessed by the investigator in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

5.5.1. Adverse Events

5.5.1.1. Definitions

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 and potential AESI cases which will be captured and tabulated in the outputs covering the whole study period. Unsolicited non-serious adverse events collected outside the 28-day period following the vaccination will be presented through listings.

For AESI analyses, the following subcategories are defined:

- Potential AESIs as identified by the investigator
- Potential AESIs selected programmatically
 - Those include all reported AEs that are identified by the selection rule:
 - SMQ (Standardised MedDRA Queries) = “EMBOLIC AND THROMBOTIC EVENTS (SMQ)”
 - or

- (SUB_SMQ1 = “HAEMATOPOIETIC THROMBOCYTOPENIA (SMQ)” and SCOPE in (“BROAD”, “NARROW”)) or HLT (higher level term)=“Thrombocytopenias”
- Potential AESIs qualified for assessment

Potential AESIs (programmed/CRF) that have risk levels assessed by one of the following three criteria are considered 'qualified for assessment':

 - Brighton Collaboration Level (Level 1-5)
 - CDC Tier (non-tier 1/ 2, tier 1, tier 2)
 - PRAC criteria (confirmed, possible, probable, unlikely, criteria not met)

Solicited administration site symptoms will be by definition considered as related to the study vaccine.

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

5.5.1.2. Analysis of Adverse Events

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. AESI analyses will be summarized by Interest Category 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 sensitivity analysis for the solicited adverse events will be done. A summary table will be provided by completeness status of e-diary (fully completed e-diary versus not or partially completed e-diary).

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

Moreover, table with Covid AEs, potential AESI as identified by the investigator, potential AESIs selected programmatically and potential AESI qualified for assessment will be created.

Potential AESIs selected programmatically will be tabulated by categories: ‘*Emolic and thrombotic events (SMQ)*’ and ‘*Haematopoietic Thrombocytopenias (SMQ) (broad) or HLT = Thrombocytopenias*’. Potential AESI determined programmatically, related to study vaccine (investigator assessment), will be tabulated similarly.

Potential AESIs as identified by the investigator, will be tabulated by categories: '*Embotolic and thrombotic events (SMQ)*' and '*Haematopoietic Thrombocytopenias (SMQ) (broad) or HLT = Thrombocytopenias*', and '*Other*'. Potential AESI as identified by the investigator, related to study vaccine (investigator assessment), will be tabulated similarly.

Potential AESIs qualified for assessment will be tabulated by categories: '*Embotolic and thrombotic events (SMQ)*' and '*Haematopoietic Thrombocytopenia (SMQ) (broad) or HLT=Thrombocytopenias*'.

All AESI analyses will be presented by phase as well as by time interval. The definition of the different time intervals can be found in Section 5.1.2.

For AESI analyses, attribution to the intervals will be done similarly to the unsolicited AEs as described in Section 5.5.1.3. For Step 2 of phase allocation of adverse events, the '0 - 28 days post-dose' interval should be treated similar to 'active' periods and the rest as 'non- active' periods. Note that the '>6 months' time-interval will only be included in listings.

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

5.5.1.3. Phase Allocation of Adverse Events

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.
- 5) In case a non-active period is followed by another non-active period, and the overlapping/consecutive events start in both periods, they are allocated to the first period and 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.

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.

5.5.1.4. Missing 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.

5.5.2. Vital Signs

Baseline and emerging vital signs abnormalities after vaccination will be listed based on the abnormality gradings in [Appendix 5](#) (Section 6.5). 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.

5.6. Other Analyses

5.6.1. Definition of Subgroups

No subgroup analysis is planned for this study.

5.7. Interim Analyses

There is no interim analysis planned before the primary analysis.

5.7.1. Independent Data Monitoring Committee (IDMC)

An IDMC will be installed to monitor the safety of participants in the ongoing Phase 3 studies.

There are no planned IDMC reviews in the current study. Safety issues that might arise from this study may be escalated to an IDMC.

If a safety issue arises, the team might request an adhoc safety review by the IDMC. This review would be based on a snapshot of the database which might not have been completely cleaned. Data will be cleaned on an ongoing basis. The IDMC will review unblinded data; the data package to be reviewed (summary data) will display the real vaccine identity. The study team will transfer the blinded data to the statistical support group (SSG), and the IWRS vendor or Secure Data vendor will securely transfer the unblinded randomization data to the SSG. In principle, there will be no meeting unless this is requested by one of the IDMC members or by the Sponsor.

Conclusions from the IDMC reviews will be communicated to the Sponsor.

The IDMC data package (summary data) will follow the same statistical methods described in this SAP. Depending on the safety issue, the IDMC data package will consist of one or more of the following tabulations: participant disposition and demographics, SAEs, related SAEs, fatal AEs, related fatal AEs, solicited and unsolicited grade 3 AEs, related AEs and AEs leading to

discontinuation. Potential AESI qualified for assessment will be listed. Other safety summaries might be requested as well. A separate IDMC DPS document will be provided to describe the specifications of the individual tables to be generated should a safety issue arise.

Data packages will be distributed by the SSG to the IDMC members via a secure electronic environment. A separate data package might be made available to the study team where the summary data are presented for the pooled groups (blinded).

The role and responsibilities of the IDMC and SSG are detailed in the IDMC charter (Section 5).

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
ATC	anatomic and therapeutic class
BMI	body mass index
CI	confidence interval
CoAd	coadministration
COVID-19	coronavirus disease-2019
CTP	clinical trial protocol
IDMC	Independent Data Monitoring Committee
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
GMT	geometric mean titre
HI	hemagglutination inhibition
LLOQ	lower limit of quantification
PPII	Per-protocol Influenza Immunogenicity
PPRI	Per-protocol RSV Immunogenicity
Pre-F	prefusion conformation-stabilized F protein
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SSG	statistical support group
ULOQ	upper limit of quantification

6.2. Appendix 2: Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

[Table 7](#) presents a list of the demographic variables that will be summarized by vaccine regimen and overall for the FAS.

Table 7: 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 (65-74 years, 75-84 years, >=85 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, intersex, unknown)	
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 (<18.5 kg/m ² [underweight], 18.5-24.9 kg/m ² [normal or healthy weight], 25.0-29.9 kg/m ² [overweight], >=30.0 kg/m ² [obese])	
Risk level of severe RSV disease (Increased risk / Non-increased risk) as collected (CDC definition)	
COVID vaccination ^b (AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine, Moderna COVID-19 vaccine, Pfizer COVID-19 vaccine, Other COVID-19 vaccine, No COVID-19 vaccination)	

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

^b Subjects can have taken multiple vaccinations, categories are not mutually exclusive.

6.3. Appendix 3: Protocol Deviations

Major protocol deviations will be summarized.

In general, a list of major protocol deviations that may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study will be specified in a major protocol violation criteria document. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category. In addition, minor and major protocol deviations related to COVID-19 will be tabulated.

6.4. Appendix 4: 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 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. Tables will be created for all concomitant medications and concomitant medications of special interest.

6.5. Appendix 5: Toxicity Grading Scale for Vital Signs

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

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 – 160 [#]	> 160 [#]	Hospitalization for malignant hypertension [#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension [#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock [#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.

** For oral temperature: no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

[#] Revised by the sponsor.

For the vital signs analysis in Section 5.5.2, only values will be used to assign abnormalities, no clinical interpretations will be used. Therefore, grade 3 and 4 will be combined because grade 4 always requires clinical interpretation.

7. REFERENCES

http://www.whocc.no/atc_ddd_index/