Janssen Vaccines & Prevention B.V.

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Safety and Immunogenicity of an Ad26.RSV.preF-based Vaccine in Adults Aged 18 to 59 Years, Including Those at High-risk for Severe RSV

Protocol VAC18193RSV3006; Phase 3

VAC18193 (JNJ-64400141/JNJ-64213175)

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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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AMENDMENT HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	21 September 2021	Not Applicable	Initial release
1.1	11 July 2022	Section 4, clarification of "as-treated" with respect to cohort assignment. Section 5.3.2, specification of the weighting approach to use for the strata-adjusted difference in seroresponse. Sections 5.1.2. and 5.4.1, Providing details on the AESI analysis Appendix 2, mean and standard deviation were added for continuous baseline variables	Non-substantial amendment prior to Database Lock.

1. INTRODUCTION

This statistical analysis plan (SAP) contains information needed to perform the complete safety and immunogenicity analysis of the VAC18193RSV3006 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 more details on the study design, and Section 6.3 of the CTP for details on randomization and procedures for maintaining the blind.

1.3. Planned analyses

Refer to Section 9.5 of the CTP for more details on the planned analyses.

2. STATISTICAL HYPOTHESES

To demonstrate the non-inferiority of the humoral immune response to Ad26/protein preF RSV vaccine in all adults aged 18 to 59 years (Group 1+3) versus in adults aged 65 years and older (Group 5) and in high-risk adults aged 18 to 59 years (Group 3) versus in adults aged 65 years and older (Group 5) in terms of neutralizing antibody GMTs and seroresponse rates.

The following hypotheses will be tested sequentially:

Null Hypothesis 1:

- Ad26/protein preF RSV vaccine induces inferior humoral immune response in terms of VNA A2 antibody GMTs at Day 15 in adults aged 18 to 59 years (Groups 1 and 3) versus in adults aged 65 years and older (Group 5).

  OR

- Ad26/protein preF RSV vaccine induces inferior humoral immune response in terms of seroresponse rates of VNA A2 antibody titers at Day 15 in adults aged 18 to 59 years (Groups 1 and 3) versus in adults aged 65 years and older (Group 5).

Alternative Hypothesis 1:

- Ad26/protein preF RSV vaccine induces non-inferior humoral responses in terms of VNA A2 antibody GMTs at Day 15 in adults aged 18 to 59 years (Groups 1 and 3) versus in adults aged 65 years and older (Group 5).

  AND

- Ad26/protein preF RSV vaccine induces non-inferior humoral responses in terms of seroresponse rates of VNA A2 antibody titers at Day 15 in adults aged 18 to 59 years (Groups 1 and 3) versus in adults aged 65 years and older (Group 5).

Success Criterion 1 (All Adults):

Non-inferiority of immune response in all adults is demonstrated:

- if the lower limit of the 2-sided 95% confidence interval (CI) for the VNA A2 GMT ratio of all adults aged 18 to 59 years versus in adults aged 65 years and older ($GMT_{Group\ 1+3}/GMT_{Group\ 5}$) is >0.67.

  AND

- if the lower limit of the 2-sided 95% CI for the seroresponse rate difference of all adults aged 18 to 59 years versus in adults aged 65 years and older (Seroresponse Rate $_{Group\ 1+3}$ − Seroresponse Rate $_{Group\ 5}$) based on the VNA A2 antibody titers is >-10%[a].

If non-inferiority is demonstrated in all adults for both neutralizing antibody GMTs and seroresponse rates, then the following hypothesis will be tested:

Null Hypothesis 2:

- Ad26/protein preF RSV vaccine induces inferior humoral response in terms of VNA A2 antibody GMTs at Day 15 in high-risk adults aged 18 to 59 years (Group 3) versus in adults aged 65 years and older (Group 5).

  OR

- Ad26/protein preF RSV vaccine induces inferior humoral response in terms of seroresponse rates of VNA A2 antibody titers at Day 15 in high-risk adults aged 18 to 59 years (Group 3) versus in adults aged 65 years and older (Group 5).

Alternative Hypothesis 2:

- Ad26/protein preF RSV vaccine induces non-inferior humoral response in terms of VNA A2 antibody GMTs at Day 15 in high-risk adults aged 18 to 59 years (Group 3) versus in adults aged 65 years and older (Group 5)

  AND

- Ad26/protein preF RSV vaccine induces non-inferior humoral response in terms of seroresponse rates of VNA A2 antibody titers at Day 15 in high-risk adults aged 18 to 59 years (Groups 3) versus in adults aged 65 years and older (Group 5).

Success Criterion 2 (High-risk Adults):

Non-inferiority of immune response in high-risk adults is demonstrated:

- if the lower limit of the 2-sided 95% CI for the VNA A2 GMT ratio of high-risk adults aged 18 to 59 years versus in adults aged 65 years and older ($GMT_{Group\ 3}/GMT_{Group\ 5}$) is >0.67.

[a] Note that the boundary of -0.1 on the proportion scale is equivalent to -10% on the percentage scale.

AND

- if the lower limit of the 2-sided 95% CI for the seroresponse rate difference of high-risk adults aged 18 to 59 years versus in adults aged 65 years and older (Seroresponse Rate $_{\text{Group 3}}$ − Seroresponse Rate $_{\text{Group 5}}$) based on the VNA A2 antibody titers is >-10%[a].

3. SAMPLE SIZE DETERMINATION

Refer to Section 9.2 of the CTP.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For vaccine studies, study intervention assignment and, for this study, cohort assignment, will follow the as treated principle. Study participants will be analyzed according to the actual vaccine regimen received and their actual age and risk level (versus what they have been assigned at randomization).

Table 2: Analysis Sets

Analysis Sets	Description
All Screened	This analysis set includes all participants screened for the study, regardless if they were screen failures or they got enrolled in the study. Rescreened participants are counted only once.
Full Analysis Set (FAS)	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 (study vaccine or placebo). All safety and participant information analyses will be based on the FAS.
Per Protocol Immunogenicity Analysis Set (PPI)	The Per Protocol Immunogenicity Analysis Set will include all randomized participants who received study vaccine and for whom immunogenicity data are available. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPI analysis. 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. The primary analysis set for analyses related to RSV immunogenicity is the PPI Set. As a sensitivity analysis, key tables may also be based on the FA Set.

[a] Note that the boundary of -0.1 on the proportion scale is equivalent to -10% on the percentage scale.

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 vaccination on Day 1. If there was no immunogenicity assessment done pre-vaccination, the assessment post-vaccination on Day 1 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 ≥ 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).

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	Date and time of 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) maximum of (28 days after vaccination at 23:59, scheduled visit 28 days after vaccination at 23:59)
Follow-up	3			One minute after Post-dose 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.

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 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.

Table 4: Definition of intervals

Dose	Interval	From	to
Post-vaccination	0 - 28 days post dose	Date time of the 1st vaccination	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum (Date of Vaccination 1 + 28 days at 23:59, date of scheduled visit 4 weeks after 1st vaccination at 23:59)
	29 - 56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 1 + 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: • 23:59 at date of last contact (for discontinuations/completions) • 23:59 at date of DB cut-off for interim analyses

5.1.3. Immunogenicity 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 below) will not be included in the per-protocol immunogenicity analysis. However, they may be included in sensitivity analyses.

Table 5: Immunogenicity timepoints

Analysis timepoint	Reference day	Target day (counted from the reference day)	Window
Baseline	Day of vaccination 1	1	(-inf, 1]
Day 15	Day of vaccination 1	15	[12, 18]
Day 183	Day of vaccination 1	183	[169, 197]

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
- 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 Immunogenicity Endpoint Analysis

5.3.1. Definition of Endpoint

The primary immunogenicity endpoints are:

- Neutralizing antibody titers against RSV A2 strain at 14 days after vaccination
- Seroresponse rate* at 14 days after vaccination as determined by neutralization assay (VNA-A2)

* Seroresponse is defined as a 4-fold increase from baseline in Day 15 VNA A2 antibody titers.

The statistical hypotheses are described in Section 2.

5.3.2. Analysis Methods

The primary immunogenicity objectives will be assessed sequentially.

To assess non-inferiority in terms of GMTs, 2-sided CIs will be calculated for the difference in $\log_2$-transformed VNA A2 antibody titers at 14 days after active vaccination between all adults aged 18 to 59 years (Groups 1 and 3) and adults aged 65 years and older (Group 5) and between high-risk adults aged 18 to 59 years (Group 3) and adults aged 65 years and older (Group 5). The GMT ratio and CIs for the neutralizing antibody GMT objectives will be calculated via an analysis of variance (ANOVA) including both active groups (ie, Groups 1, 3, and 5) with Day 15 (ie, 14 days after vaccination) VNA A2 antibody titers as dependent variable and group as independent variable and COVID-19 vaccination as a stratification factor (3 categories: 1. Janssen COVID-19 vaccine, 2. Vaxzevria (Oxford/AstraZeneca), 3. other vaccine, or no vaccine). The CIs around the

difference will be back-transformed (by exponentiation) to CIs around a GMT ratio ($GMT_{Group\ x}/GMT_{Group\ 5}$, with x=1+3 or x=3) and compared to the non-inferiority limit of 0.67 (2/3).

To assess non-inferiority in terms of seroresponse rates (co-primary objective), 2-sided CIs will be calculated for the difference in seroresponse rates 14 days after active vaccination for the same comparisons. Seroresponse based on VNA A2 antibody titers is defined as a 4-fold increase from baseline on Day 15. The Newcombe (Score) with continuity correction method will be used to calculate the CIs for the difference in seroresponse rates (Seroresponse Rate $_{Group\ x}$ – Seroresponse Rate $_{Group\ 5}$, with x=1+3 or x=3) in percentage and compared with the non-inferiority margin of -10%. This analysis will be stratified for COVID-19 vaccination, applying Cochran-Mantel-Haenszel weightings to yield a strata-adjusted difference in seroresponse.

Non-inferiority of the humoral immune response to Ad26/protein preF RSV vaccine in all adults aged 18 to 59 years (Groups 1 and 3) versus in adults aged 65 years and older (Group 5) is demonstrated if the lower limit of the 2-sided 95% CI of the estimated GMT ratio is >0.67 and if the lower limit of the 2-sided 95% CI of the estimated difference in seroresponse rate is >-10%.

If non-inferiority in all adults aged 18 to 59 years (Groups 1 and 3) is not demonstrated for both neutralizing antibody GMTs and seroresponse rates, the study fails. If non-inferiority in all adults aged 18 to 59 years is demonstrated for both neutralizing antibody GMTs and seroresponse rates, then non-inferiority in high-risk adults aged 18 to 59 years (Group 3) can be tested, similarly as the comparison between all adults aged 18 to 59 years (Groups 1 and 3) and adults aged 65 years and older (Group 5), stratified for COVID-19 vaccination. Non-inferiority of the humoral immune response to Ad26/protein preF RSV vaccine in high-risk adults aged 18 to 59 years (Group 3) versus in adults aged 65 years and older (Group 5) is demonstrated if the lower limit of the 2-sided 95% CI of the estimated GMT ratio is >0.67 and if the lower limit of the 2-sided 95% CI of the estimated difference in seroresponse rate is >-10%.

As a sensitivity analysis to assess the impact of baseline titers, the neutralizing antibody GMT primary endpoint will also be evaluated adjusting for the respective baseline titers. For immunogenicity, baseline is considered as the last assessment pre-vaccination. In a second sensitivity analysis, different variances between the groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

The significance level (α) is 5% (2-sided). No multiplicity adjustments are needed since the cohorts are tested sequentially in the overall 18 to 59 years group (Groups 1 and 3) followed by the high risk 18 to 59 years group (Group 3) and since non-inferiority based on GMTs and seroresponse rate both need to be met for each comparison, and as no interim analyses are planned before the primary analysis.

The population for analyses related RSV immunogenicity is the PPI set. 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, values below LLOQ will be imputed to LLOQ.
- Data above the ULOQ will be imputed with the ULOQ.

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

5.4. Primary Safety Endpoint Analysis

Safety endpoints include:

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

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by cohort and group. All safety analyses will be based on the FA Set. 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.

Safety data will be analyzed by study intervention regimens as designed per protocol, per phase and across the entire study period where applicable. For unsolicited AE, 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 PI in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

5.4.1. Adverse Events

5.4.1.1. 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, 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.

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.

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)

5.4.1.2. 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 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 post-dose period.

For unsolicited AEs following tables will be provided: summary table (including SAE, fatal outcome, AESI, AE leading to study discontinuation), all events, most frequent, at least grade 3, related, 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: 'Embolic and thrombotic events (SMQ)' and 'Haematopoietic Thrombocytopenia (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: *'Embolic and thrombotic events (SMQ)'* and *'Haematopoietic Thrombocytopenia (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: 'Embolic 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 5.4.1.3. 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.

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

5.4.1.3. 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 ADAM (Analysis Data Model) 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 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 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 (ie 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 period), except if the end date of the AE falls before the start of the first active phase (Post-dose 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.

5.4.1.4. 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.

5.4.2. Vital Signs

Baseline and emerging vital sign abnormalities will be listed based on the abnormality gradings in Appendix 5. An abnormality will be considered as emerging if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging.

5.5. Secondary and Exploratory Immunogenicity Endpoints Analysis

5.5.1. Secondary and Exploratory Immunogenicity Endpoint(s)

Humoral and cellular immune responses against the insert are measured. The measured humoral immune responses include titers of neutralizing antibodies and binding antibody titers (ELISA). The measured cell-mediated immune responses include RSV specific INFγ ELISpot responses and intracellular cytokine staining (ICS) if available. Immunogenicity against the vector will be explored using an adenovirus neutralization assay.

Immunogenicity responses will be summarized per cohort and group.

Note: Exploratory endpoints are optional. Exploratory assessments are based on the outcome of ongoing testing in other studies. Some testing may not be performed or reported.

5.5.1.1. 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 treated differently according to the assay:

- For all humoral assays, the same rules as described in Section 5.3.3 will be used.
- For ELISpot assays: the LLOQ will be used if available and validated, the same rules as described in Section 5.3.3 will be used.
- For ICS assays: the LLOQ will be used if available and validated. In case no validated LLOQ is available then a provisional cut-off will be provided before DBL (only for total cytokine response), in the database. The same rules as described in Section 5.3.3 will be used. For the individual cytokine combinations of IFNγ, TNFa and IL2, if available, negative values will be imputed with 0.

Data above the ULOQ will be imputed with the ULOQ.

5.5.1.2. Immunogenicity Against the Insert:

5.5.1.2.1. Humoral assays

For **VNA** and **ELISA** assays following results will be calculated: N, geometric mean[§] and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented. *[§]calculate the mean and corresponding 95%CI of the log_2 transformed values, back-transform this mean [ie 2^mean] and CI [ie 2^CI].*

Actual values and fold changes from baseline are tabulated and shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay. In addition, Geometric Mean Titres (GMT) plots over time, combining the regimens in one graph (without individual participant dots) will also be created.

Reverse distribution curves of the actual values are provided for all time points.

In the graphs, original values will be displayed on the log_2 scale.

Scatterplots with the VNA versus ELISA will be provided for the different time points. In these scatterplots the actual values will be shown, even if they are below the LLOQ, but the LLOQ cut-off will be visualized in the graph per assay if some values are below LLOQ.

For pre-F ELISA, the percentages of participants with 2- and 4-fold increase from baseline will also be tabulated.

GMT ratios and 95% CIs of all adults aged 18 to 59 years (Groups 1 and 3) versus adults aged 65 years and older (Group 5) and high-risk adults aged 18 to 59 years (Group 3) versus adults aged 65 years and older (Group 5) may be calculated for other VNA A2 timepoints and for other humoral assays, similarly to the primary endpoint.

Moreover, the difference in seroresponse rates for the same comparisons may be calculated for other VNA A2 timepoints and other humoral assays, similarly to the primary endpoint.

5.5.1.2.2. Cellular assays

For **ELISpot** following results will be calculated: N, median, quartiles and range of the actual values will be tabulated and graphically presented.

Tables with the corresponding descriptive statistics will be provided.

Actual values are shown as box plots with dots for participant values, and the corresponding median and interquartile range per time point for each assay. In addition, box plots over time, combining the regimens in one graph (without individual participant dots) will also be created. For the graphs, original values will be displayed on the log_{10} scale.

For **ICS** and **PBMC secreted cytokines** (if available) possible analyses may include:

- Total Cytokine response: the % of subsets expressing at least IFN-γ, TNF-α, or IL-2 will be calculated for CD4 and CD8.

  Tables with the corresponding descriptive statistics will be provided.

  Actual values are shown as box plots with dots for participant values, and the corresponding median and interquartile range per time point for each assay.

  In addition, box plots over time, combining the regimens in one graph (without individual participant dots) will also be created.

- For all cytokine combinations (IFN-γ, TNF-α, or IL-2) bar charts reflecting the median magnitude of each combination will be graphically presented. Tables with the corresponding descriptive statistics will be provided.
- Th1 and Th2: Th1 is defined as %RSV-F specific CD4 T-cells IFNγ+ AND/OR IL2+ and Th2 as %RSV-F specific CD4 T-cells IL4+ AND/OR IL13+ AND CD40L+. Subject profiles and graphs of the actual values over time (box-plot type) will be created. In addition, at time points of interest, scatterplots of Th1 vs Th2 might be created.

For the graphs, original values will be displayed on the $\log_{10}$ scale.

Scatterplot with humoral and cellular assays may be provided for the most important time points.

Technical details for the calculation of the ICS values to be used in the graphs will be part of the DPS.

5.5.1.3. Immunogenicity Against the Vector

For **Ad26-specific VNA** following statistics will be calculated: N, geometric mean. *§calculate the mean and corresponding 95%CI of the $\log_{10}$ transformed values, back-transform this mean [ie 10^mean] and CI [ie 10^CI].* and corresponding 95% CI of the actual values.

Participant profiles of the assays against the insert will be repeated, highlighting participants with pre-existing immunity at baseline against the vectors.

Scatterplots with the Adeno assays versus the assays against the inserts will be provided for all timepoints. In these scatterplots the actual values will be shown, even if they are below the LLOQ.

For the graphs, Ad26-specific VNA values will be displayed on the $\log_{10}$ scale.

5.6. Other Analyses

5.6.1. Definition of Subgroups

The following subgroups will be investigated for summary immunogenicity and safety analyses, for Cohorts 1 and 2 only:

- 18-49 years and 50-59 years

5.7. Interim Analyses

There is no interim analysis planned before the primary analysis.

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

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 and related AEs. 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 roles 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

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ANOVA	Analysis of Variance
ATC	anatomic and therapeutic class
BCC	Brighton Collaboration Case Definition
BMI	body mass index
CDC	Center for Disease Control and Prevention
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
DMC	Data Monitoring Committee
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FAS	full analysis set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GMC	geometric mean antibody concentration
GMI	Geometric Mean Increase
GMT	Geometric Mean Titrer
HR	hazard ratio
ICF	informed consent form
ICS	intracellular cytokine staining
IFNg	interferon gamma
IL2	interleukin 2
IRR	incidence rate ratio
ITT	intent-to-treat
IWRS	interactive web response system
LLOQ	lower limit of quantification
NA	not applicable
PBMC	peripheral blood mononuclear cells
PP	per protocol efficacy analysis set
PPI	per protocol immunogenicity analysis set
PRAC	Pharmacovigilance Risk Assessment Committee
Pre F	prefusion conformation-stabilized F protein
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SFU	spot forming units
TNFa	tumor necrosis factor alpha
ULOQ	upper limit of quantification
VE	vaccine efficacy
VNA	virus neutralizing antibody
WHO	World Health Organization

6.2. Appendix 2 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 6 presents a list of the demographic variables that will be summarized by vaccine regimen and overall, for the FAS.

Table 6: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation, median and minimum and maximum).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables	
Age (18-45, 46-59, 65-74 years, 75-84 years, >=85 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 (<18.5 kg/m2 (underweight), 18.5-24.9 kg/m2 (Normal or Healthy weight), 25.0-29.9 kg/m2 (Overweight), ≥30.0 kg/m2 (Obese))	
Risk level of severe RSV disease (Increased risk / Non-increased risk) as collected (CDC definition)	
Covid vaccination at baseline (Janssen COVID-19 vaccine, AstraZeneca COVID-19 vaccine,, Moderna COVID-19 vaccine, Pfizer COVID-19 vaccine, Other COVID-19 vaccine, No COVID-19 vaccine)	

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

6.3. Appendix 3 Protocol Deviations

Major protocol deviations will be summarized.

In general, a 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. 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 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, started during the 8 days following 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 medication and concomitant medications of special interest.

6.5. Appendix 5 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

For Cohort 1 and Cohort 2:

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 – 155	> 155	Hospitalization for malignant hypertension#
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension#
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock#
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

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

For Cohort 3:

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#

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
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.
[##] Modified upper limit regarding the participant population (participants aged 60 years and older).

For the vital signs analysis in Section 5.4.2 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.

6.6. Appendix 6 Changes to the planned analysis

No changes to the planned analysis.

7. REFERENCES

WHO Collaborating Centre for Drug Statistics: ATC/DDD Index 2021. Available from: https://www.whocc.no/atc_ddd_index/