**Janssen Vaccines & Prevention B.V.**

**Statistical Analysis Plan**

# A Randomized, Double-blind Phase 3 Study to Compare the Immunogenicity of Clinical Trial Material of an Ad26.RSV.preF-based Vaccine for Phase 3 with Clinical Trial Material Representative of Phase 2b in Adults Aged 60 to 75 Years

**Protocol VAC18193RSV3004; Phase 3**

**VAC18193 (JNJ-64400141/JNJ-64213175)**

**Status:** Approved
**Date:** 07 July 2022
**Prepared by:** Janssen Vaccines & Prevention B.V.
**Document No.:** EDMS-RIM-433281, 2.0

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

# TABLE OF CONTENTS

# AMENDMENT HISTORY

**Table 1: SAP Version History Summary**

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1.0 | 27 September 2021 | Not Applicable | Initial release |
| 2.0 | 07 July 2022 | 1) the upper age limit was changed from less than 65 years to 75 years inclusive<br>2) mean and standard deviation was added for continues baseline variables<br>3) Methods for analyses of AESIs were added | To align with the CTP Amendment 2<br><br>To better see the differences between groups in baseline characteristics<br>Algorithms to describe AESIs were specified |

# 1. INTRODUCTION

This statistical analysis plan (SAP) contains information needed to perform the complete safety and immunogenicity analysis of the VAC18193RSV3004 trial. It applies to all the analyses described in Section 9.4 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

Please 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.

# 2. STATISTICAL HYPOTHESES

To demonstrate non-inferiority in terms of humoral immune responses induced by vaccination with one dose of the Phase 3 CTM compared with one dose of the Phase 2b CTM, the following hypotheses will be tested:

***Null Hypothesis:***

The Phase 3 CTM induces inferior GMTs of the pre-F ELISA titers on Day 15, compared with the Phase 2b CTM.

***Alternative Hypothesis:***

The Phase 3 CTM induces non-inferior GMTs of the pre-F ELISA titers on Day 15, compared with the Phase 2b CTM.

Non-inferiority will be shown if the lower limit of the 2-sided 95% CI around the estimated GMR (Phase 3 CTM versus the Phase 2b CTM) lies entirely above 0.67.

# 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.

**Table 2: Analysis Sets**

| Analysis Set | 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.<br><br>Rescreened participants are counted only once. |
| Full Analysis Set (FAS) | The full analysis set (FAS) will include all participants who received study vaccination, regardless of the occurrence of protocol deviations and vaccine type (study vaccine or placebo).<br><br>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 experienced a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPI analysis.<br><br>The list of major protocol deviations that would lead to elimination from the immunogenicity analysis is specified in the major protocol violation criteria document, which will be finalized before database lock and unblinding.<br><br>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 FAS. |

# 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 vaccination).
- Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of 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 the Post-dose period |
| Regimen | 2 | Post-dose | 1 | Date and time of first vaccination | Minimum of:<br>a) 23:59 at the date of last contact (for early discontinuation)<br>b) 23:59 at the database cut-off date for analyses conducted before the final analysis<br>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:<br>a) 23:59 at the date of last contact (for early discontinuation or participants that completed the study)<br>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:<br>• 23:59 at date of last contact (for discontinuations)<br>• 23:59 at date of DB cut-off for interim analyses<br>• Maximum(Date of Vaccination 2 + 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:<br>• 23:59 at date of last contact (for discontinuations)<br>• 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:<br>• 23:59 at date of last contact (for discontinuations)<br>• 23:59 at date of DB cut-off for interim analyses<br>• Date of Vaccination 1 + 183 days at 23:59 |

### 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 | (-∞, 1] |
| Day 15 | Day of vaccination 1 | 15 | [12, 18] |

## 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 not randomized and not vaccinated
- participants not randomized and vaccinated
- participants 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 3, Appendix 4 and Appendix 5, respectively. Medical history and concomitant diseases will be tabulated.

## 5.3. Primary Endpoint(s) Analysis

### 5.3.1. Definition of Endpoint(s)

The primary endpoint is the pre-F enzyme-linked immunosorbent assay (ELISA) antibody titer at 14 days after vaccination.

### 5.3.2. Analysis Methods

The primary immunogenicity objective will be assessed by calculating the 2-sided 95% CIs for the difference in log-transformed Day 15 pre-F ELISA titers (ie, Group 1 versus Group 2).

The CI will be calculated via an analysis of variance (ANOVA) including both groups with Day 15 pre-F ELISA titers as dependent variable and group as independent variable. The CIs around the difference will be back-transformed (by exponentiation) to CIs around a GMR ($GMT_{\text{Phase 3 CTM}}/GMT_{\text{Phase 2b CTM}}$) and compared to the non-inferiority limits of 0.67 (2/3).

Non-inferiority between the Phase 3 CTM versus the Phase 2b CTM is demonstrated if the lower limit of the 2-sided 95% CI of the estimated GMR lies entirely above 0.67.

As a sensitivity analysis to assess the impact of baseline titers, the 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). As no interim analyses before the primary analysis are planned, no multiplicity adjustments are needed.

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 $log_2$ transformed values, back-transform this mean [ie 2^mean] and CI [ie 2^CI].*

The tables will also show the fold increases together with the percentage of participants with a 2- and a 4 -fold increase from baseline.

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. In addition, plots of GMT over time, combining the regimens in one graph (without individual participant dots) will be created. Reverse distribution curves of the actual values will be provided, for baseline and Day 15. In the graphs, original values will be displayed on the $log_2$ scale.

### 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. Secondary Endpoint

### 5.4.1. Definition of Endpoint(s)

The secondary endpoint is RSV virus neutralization antibody (VNA A2) titers at 14 days after vaccination.

### 5.4.2. Analysis Methods

VNA A2 titers will be analyzed descriptively. Descriptive statistics of the actual values (geometric mean and 95% CI) will be calculated at all timepoints. Additionally, geometric mean fold increases from baseline and corresponding 95% CIs will be calculated, as well as the percentage of participants with 2- and 4- fold increases from baseline.

Graphical representations will be created as applicable.

Geometric mean fold rises (GMT Phase3 CTM/GMT Phase 2b CTM) might also be calculated in a similar manner as for pre-F ELISA.

### 5.4.3. 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 as described in Section 5.3.3.

## 5.5. Safety Analyses

Safety endpoints (secondary endpoints):

- Solicited local (injection site) and systemic AEs for 7 days after vaccination
- Unsolicited AEs for 28 days after vaccination
- SAEs and AESIs until 6 months after 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 analyzed by study intervention regimens as designed per protocol, per phase and also 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 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 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 by definition will be 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 post-dose period.

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

Moreover, table with Covid-19 related 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 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: '*Embolic 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: '*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 5.5.1.3. 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.

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 AESIs.

#### 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 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.

#### 5.5.1.4. 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 sign abnormalities will be listed based on the abnormality gradings in Appendix 6. 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.

## 5.6. 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. Data Monitoring Committee (DMC) or Other Review Board

An Independent DMC (IDMC) will be installed to monitor the safety of participants in the ongoing VAC18193 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 ad hoc 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 AESIs qualified for assessment and potential AESI 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 Section 5 of the IDMC charter.

# 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 |
| CI | confidence interval |
| CRF | case report form |
| CTM | clinical trial material |
| 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 |
| GMT | Geometric Mean Titer |
| ICF | informed consent form |
| ICS | intracellular cytokine staining |
| IDMC | Independent Data Monitoring Committee |
| IWRS | interactive web response system |
| LLOQ | lower limit of quantification |
| NA | not applicable |
| PPI | per protocol immunogenicity analysis set |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| Pre F | prefusion conformation-stabilized F protein |
| RSV | respiratory syncytial virus |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SDTM | Study Data Tabulation Model |
| SE | standard error |
| ULOQ | upper limit of quantification |
| VNA | virus neutralization assay |
| WHO | World Health Organization |

## 6.2. Appendix 2 Changes to Protocol-Planned Analyses

No changes to planned analysis.

## 6.3. Appendix 3 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:** | |
| Sex (male, female, unknown, intersex) | Frequency distribution with the number and percentage of participants in each category. |
| 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), 25-29.9 kg/m2 (Overweight), ≥30 kg/m2 (Obese) ) | |
| Risk level of severe RSV disease (Increased risk / Non-increased risk) as collected (CDC definition) | |
| COVID vaccination[b] at baseline (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.

## 6.4. Appendix 4 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.

## 6.5. 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 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 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 medication and concomitant medications of special interest.

## 6.6. Appendix 6 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

*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) **<br>(°F) ** | 38.0 – 38.4<br>100.4 – 101.1 | 38.5 – 38.9<br>101.2 – 102.0 | 39.0 – 40<br>102.1 – 104.0 | > 40<br>> 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 | ER visit or 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.
** 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

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