# SAP Core Body

**Title:** Phase II, randomized, observer-blind, placebo-controlled, multi-center study of a live-attenuated Respiratory Syncytial Virus vaccine to assess the vaccine virus' transmissibility in household or daycare center settings, shedding, and genetic stability, and to describe the immunogenicity and safety of the vaccine in infants and toddlers 6 to < 24 months of age

**Study Code:** VAD00014

**Study Phase:** II

**SAP Core Body Version:** 1.0

**SAP Core Body Date:** 17 Oct 2023

**Protocol Version Number:** 4.0

The SAP Code Body should be used in conjunction of the study protocol and the SAP TLF (if applicable).

## Version History

Not applicable as this is the first version of the SAP Core Body.

# Table of Contents

# List of Tables

# List of Figures

# 1 Overall Design

In the context of intranasal administration of a live attenuated Respiratory Syncytial Virus (RSV) vaccine and to demonstrate that a large-scale study with the RSVt vaccine can be conducted safely, both the transmission rate and the genetic stability of the vaccine virus will be determined. In addition, the vaccine virus shedding will be described in the RSVt vaccinees at regular timepoints and the clinical safety in their close contacts will be assessed.

Data generated in the VAD00014 study will provide insights into the transmission of the RSVt vaccine virus and genetic stability, along with the safety and immunogenic profile of the RSVt vaccine candidate, and may support the next steps of the development, including the planned large-scale Phase III efficacy study.

The design of the study is summarized in Table 1.1 and in Figure 1.1:

**Table 1.1: Design**

| | |
|---|---|
| Type of design | Parallel, multi-center |
| Phase | II |
| Control method | Placebo-controlled |
| Study population | • Pediatric participants:<br>Healthy infants / toddlers 6 to < 24 months of age in close contact with other infants / toddlers 6 to < 24 months of age who will participate in the study<br>• Ad-hoc close contact participants:<br>Ad-hoc close contact children and adults who experience acute respiratory illness (ARI) in the 28 days following the administration of the study intervention to the close contact pediatric participant |
| Level and method of blinding | Observer-blind:<br>• Blinding for study intervention group assignment: participants, parents or legally acceptable representative (LAR), outcome assessors, investigators, laboratory personnel, Sponsor study staff<br>• No blinding for study staff who prepare and administer the study interventions |
| Study intervention assignment method | Pediatric participants will be screened for eligibility criteria at the time of inclusion and randomized to receive either RSVt vaccine or placebo in a 1:1 ratio.<br>Randomization will be stratified by contact group (the household /group attended in daycare center) and by age group (< 12 months / ≥ 12 months) |

| | |
|---|---|
| Number of participants | 100 pediatric participants 6 to < 24 months of age |
| Intervention groups | Eligible pediatric participants will be randomized in a 1:1 ratio to receive 2 intranasal administrations (56 days apart) of either the RSVt vaccine or placebo at D01 and D57 |
| Total duration of study participation | Approximately 8 months for each pediatric participant. The duration of the ad-hoc close contacts will be limited to the Illness Visit. |
| Countries | United States and Puerto Rico |
| Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group | NO |

## Table 1.2: Schedule of activities for pediatric participants

Phase II Study, 11 Planned Visits, 2 Vaccinations, 3 Blood Samples, 9 Planned Nasal Swabs, One 6-Month Safety Follow-up Phone Call, approximately 8 Months' Duration Per Pediatric Participant

| **Visit/Contact*** | **Collection of information in the CRF** | **V01** | **V02** | **V03** | **V04** | **V05** | **V06** | **V07** | **V08** | **V09** | **V10** | **V11** | **Safety followup phone call** | **Illness Visit‡‡** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study timelines days (D)** | | D01 | D04 | D08 | D11 | D15 | D18 | D22 | D57 | D64 | D71 | D85 | D237 | |
| **Visit Interval** | | | V01 + 3d | V01 + 7d | V01 + 10d | V01 + 14d | V01 + 17d | V01 + 21d | V01 + 56d | V08 + 7d | V08 + 14d | V08 + 28d | V08 + 6 months | |
| **Time windows (days)** | | NA | [+1] | [+1] | [+1] | [+1] | [+1] | [+1] | [+7] | [+1] | [+1] | [+7] | [+14] | |
| **Visit procedures:** | | | | | | | | | | | | | | |
| Informed consent | X | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | | |
| Collection of demographic data | X | | | | | | | | | | | | | |
| Collection of medical history | X Significant Medical History | X | | | | | | | | | | | | |
| Physical examination | X | X | | | | | | | X | | | | | |
| Vital signs† | X | X | | | | | | | X | | | | | |
| Rapid COVID-19 test | X | X | | | | | | | X | | | | | |

| **Visit/Contact*** | **Collection of information in the CRF** | **V01** | **V02** | **V03** | **V04** | **V05** | **V06** | **V07** | **V08** | **V09** | **V10** | **V11** | **Safety followup phone call** | **Illness Visit‡‡** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study timelines days (D)** | | D01 | D04 | D08 | D11 | D15 | D18 | D22 | D57 | D64 | D71 | D85 | D237 | |
| **Visit Interval** | | | V01 + 3d | V01 + 7d | V01 + 10d | V01 + 14d | V01 + 17d | V01 + 21d | V01 + 56d | V08 + 7d | V08 + 14d | V08 + 28d | V08 + 6 months | |
| **Time windows (days)** | | NA | [+1] | [+1] | [+1] | [+1] | [+1] | [+1] | [+7] | [+1] | [+1] | [+7] | [+14] | |
| Collection of reportable concomitant medications/vaccinations | X | | | | | | | | X | | | | | X |
| Randomization/allocation of participant number | X | X | | | | | | | | | | | | |
| Dose number | X | X | | | | | | | X | | | | | |
| Blood sampling (BL) [5 mL] | X | BL0001 Pre-vac1 | | | | | | | BL0002 Pre-vac2 | | | BL0003 | | |
| Nasal swab (NS)‡ | X | NS0001 Pre-vac1 | NS0002 | NS0003 | NS0004 | NS0005 | NS0006 | NS0007 | | NS0008 | NS0009 | | | UN0001 to UN000X |
| **Vaccination (vac)** | X | VAC1 | | | | | | | VAC2 | | | | | |
| Immediate surveillance (30 min)§ | X | X | | | | | | | X | | | | | |
| DC provided** | | DC1 | | | | | | | DC2 | | | | | |
| DC reviewed†† | | | DC1 | DC1 | DC1 | DC1 | DC1 | DC1 | DC1 | DC2 | DC2 | DC2 | | |
| DC collected | | | | | | | | | DC1 | | | DC2 | | |
| MA provided | | | | | | | | | | | | MA | | |
| MA reviewed | | | | | | | | | | | | | MA | |
| Collection of solicited administration site and systemic reactions | X | From D01 to D22 | | | | | | | From D57 to D78 | | | | | |

| Visit/Contact* | Collection of information in the CRF | V01 | V02 | V03 | V04 | V05 | V06 | V07 | V08 | V09 | V10 | V11 | Safety followup phone call | Illness Visit‡‡ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study timelines days (D)** | | D01 | D04 | D08 | D11 | D15 | D18 | D22 | D57 | D64 | D71 | D85 | D237 | |
| **Visit Interval** | | | V01 + 3d | V01 + 7d | V01 + 10d | V01 + 14d | V01 + 17d | V01 + 21d | V01 + 56d | V08 + 7d | V08 + 14d | V08 + 28d | V08 + 6 months | |
| **Time windows (days)** | | NA | [+1] | [+1] | [+1] | [+1] | [+1] | [+1] | [+7] | [+1] | [+1] | [+7] | [+14] | |
| Collection of unsolicited AEs | X | From D01 to D29 | | | | | | | From D57 to D85 | | | | | |
| Collection of AESIs and MAAEs | X | From D01 to D29 | | | | | | | From D57 to D85 | | | | | |
| Collection of SAEs | X | Throughout the study | | | | | | | | | | | | |
| Phone Call | | | | | | | | | | | | | X | |
| Collection of End of Study Intervention Phase status | X | | | | | | | | | | | X | | |
| Collection of 6-Month Follow-up-End of Study status | X | | | | | | | | | | | | X | |

Abbreviations: AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CRF, case report form; DC: diary card; LAR, legally acceptable representatives; MA, memory aid; MAAE, medically-attended adverse event; NA, not applicable; SAE, serious adverse event.

* Additional unscheduled visits may be performed for safety reasons; information will be reported in the source documents.

† Vital signs will be collected in the eCRF.

‡ All pediatric participants will provide a nasal swab sample for detection of vaccine virus shedding / transmission at specified visits. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19), if the pediatric participant is ill at the time of the visit. If needed, home visits (including Illness Visit) may be conducted by a clinical site nurse to perform the nasal swabs, except for V07, which should be done at the clinical site (as a physician should review the diary card).

§ Any unsolicited systemic adverse events occurring within the 30 minutes from study intervention administration will be recorded as immediate unsolicited systemic AE in the case report book.

** The investigator or a designee will remind the parents / LAR to bring back the DC at the next visit and will answer any questions.

The parent / LAR will record information in the DC about solicited reactions from D01 to D22, and unsolicited AEs and AESIs from D01 to D29 after each study intervention administration.

†† The investigator or a designee will interview the parents / LAR to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear. In case of home visit(s) done by a clinical site nurse, the DC will be reviewed by a physician at the next clinical site visit.

‡‡ Illness Visits: Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from pediatric participants in case of acute respiratory illness. All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship.

## Table 1.3: Schedule of activities for ad-hoc close contact participants

Phase II Study, at least 1 Unplanned Illness Visit, at least 1 Unplanned Nasal Swab, Duration is limited to the Illness Visit(s)

| **Visit (V) / Contact*** | **Collection of information in the CRF** | **Illness Visit(s)** |
|---|---|---|
| **Study timelines - Days(D)** | | **Not applicable** |
| **Visit Interval** | | **ARI** symptoms during the 28 days following any administration of the study intervention to the close contact pediatric participant** |
| **Time windows (days)** | | **Not applicable** |
| Informed consent† | X | X |
| Collection of demographic data† | X | X |
| Allocation of participant number† | X | X |
| Nasal swab (NS)‡ | X | UN0001 to UN000X§ |
| Collection of End of Study status | X | At the end of the study intervention phase for the pediatric participant in close contact to ad-hoc participant |

Abbreviations: CRF, case report form; ARI, acute respiratory illness

* Additional unscheduled visits may be performed for safety reasons; information will be reported in the source documents.

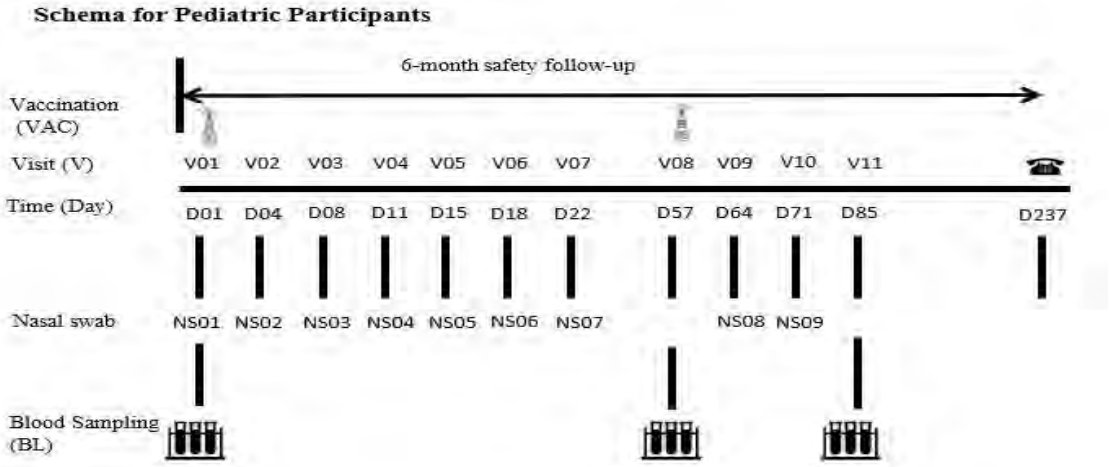
† To be collected during the first illness visit.

‡ Illness Visits: All the nasal swab specimens will be collected in the recommended viral transport media tube and will be stored between -60°C and -80°C until ready to ship.

§ Ad-hoc close contact participants will provide a nasal swab sample for detection of vaccine virus transmission. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19).

** Acute respiratory illness includes upper and lower respiratory illness

**Figure 1.1: Graphical study design**



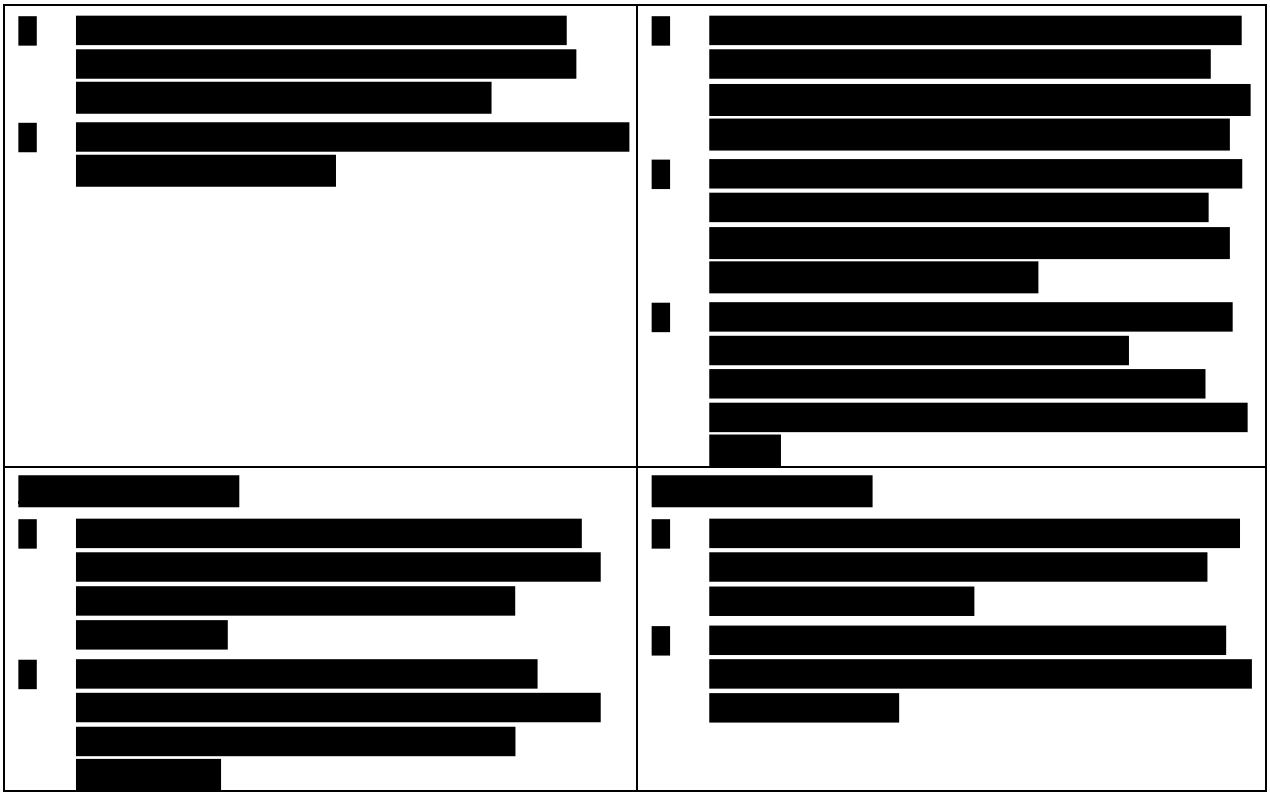

Detailed design is provided in Sections 4.1 and 1.1 of the protocol.

# 2 Objectives and Endpoints

**Table 2.1: Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To describe the vaccine virus transmission in pediatric participants receiving placebo after the first study intervention administration<br>• To describe the vaccine virus shedding in all pediatric participants with detected vaccine virus after each administration<br>• To describe the vaccine virus stability in pediatric participants receiving placebo and ad-hoc close contact participants | • Presence of vaccine virus in day (D)01, D04, D08, D11, D15, D18, and D22 nasal swabs, detected by quantitative reverse transcription polymerase chain reaction (RSVt qRT-PCR) Assay in pediatric participants receiving placebo<br>• Titer of vaccine virus shedding in D01, D04, D08, D11, D15, D18, D22, D64, and D71 nasal swabs, quantified by RSVt qRT-PCR Assay in all pediatric participants<br>• Difference in genetic sequence of mutated vaccine virus segments compared to the reference strain vaccine virus isolates in the vaccine virus positive swabs from pediatric participants receiving placebo and ad-hoc close contact participants |
| Secondary | |
| **Immunogenicity**<br>• To evaluate the RSV A serum neutralizing and RSV serum anti-F immunoglobulin G (IgG) antibody responses to the study intervention after each study intervention administration in all pediatric participants | **Immunogenicity**<br>• RSV A serum neutralizing antibody titers up to 28 days after the second administration (D01, D57, and D85)<br>• RSV serum anti-F IgG Enzyme-linked Immuno-adsorbant Assay (ELISA) antibody titers up to 28 days after the second administration (D01, D57, and D85) |
| **Safety**<br>• To assess the safety profile of the RSVt vaccine after each and any study intervention administration in pediatric participants. | **Safety**<br>• Presence of any unsolicited systemic AEs reported in the 30 minutes after each study intervention administration<br>• Presence of any solicited (ie, pre-listed in the participant's diary card [DC] and in the case |

| | |
|---|---|
| | report book [CRB]) administration site and systemic reactions within 21 days after each study intervention administration<br>• Presence of any unsolicited (spontaneously reported) AEs within 28 days after each study intervention administration<br>• Presence of any AESIs within 28 days after each study intervention administration<br>• Presence of any MAAEs within 28 days after each study intervention administration<br>• Presence of any SAEs throughout the study |
| **Transmission and virus shedding**<br>• To describe the vaccine virus transmission in pediatric participants receiving placebo after the second study intervention administration | **Transmission and virus shedding**<br>• Presence of vaccine virus in D64 and D71 nasal swabs, detected by RSVt qRT-PCR in the pediatric participants receiving placebo |
| Exploratory | |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |



# 3 Statistical Considerations

## 3.1 Statistical Hypotheses

All analyses will be descriptive, no hypothesis will be tested.

## 3.2 Sample Size Determination

No sample size calculation was done as there are no statistical hypotheses in this study. A total of 100 pediatric participants (ie, 50 per study intervention group) are planned to be enrolled, based on clinical feasibility.

## 3.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

| Participant Analysis Set | Description |
|---|---|
| Randomized | Pediatric participants for whom a study intervention group has been allocated. |
| Safety Analysis Set (SafAS) | Pediatric participants who have received at least one study intervention administration. All pediatric participants will have their safety analyzed after each vaccination according to the study intervention they actually received, and after any vaccination according to the study intervention received at the first study intervention administration.<br>Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately). |
| Full Analysis Set (FAS) | Subset of randomized pediatric participants who received at least one study intervention administration.<br>Pediatric participants will be analyzed according to the study intervention to which they were randomized. |

| | |
|---|---|
| Per-protocol analysis set (PPAS) | The PPAS is a subset of the FAS.<br>The pediatric participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:<br>• Pediatric participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria<br>• Pediatric participant did not receive first study intervention administration at D01<br>• Pediatric participant received a study intervention at D01 other than the one that he / she was randomized to receive<br>• Preparation and / or administration of study intervention at D01 not done as per-protocol<br>• Pediatric participant NOT having at least 4 nasal swabs (with a valid result) between D08 and D22, with a maximum of 5 days' time interval between 2 consecutive nasal swabs<br>• Pediatric participant received a protocol-prohibited therapy before collection of nasal swab between D08 and D22<br>• Pediatric participant with an emergency unblinding performed by the investigator before collection of nasal swab at D22<br>• Pediatric participant who was RSV- exposed before study intervention administration at D01 |
| Other analysis set | An analysis set will be used to document transmission of vaccine virus in the ad-hoc close contact participants |

## 3.4 Statistical Analyses

### 3.4.1 General Considerations

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

The results of the statistical analysis will be available in the clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

**Table 3.1: Descriptive statistics produced**

| | | |
|---|---|---|
| **Disposition and follow-up description** | **Categorical data** | Number of participants.<br>Percentage of participants. |
| | **Continuous data** | Mean, standard deviation, quartiles, minimum, and maximum. |
| **Baseline characteristics** | **Categorical data** | Number of participants.<br>Percentage of participants. |
| | **Continuous data** | Mean, standard deviation, quartiles, minimum and maximum. |
| **Clinical safety results** | **Categorical data** | Solicited: Number and percentage (95% CIs) of participants.<br>Unsolicited: Number and percentage (95% CIs) of participants and number of events. |
| **Vaccine virus shedding results** | **Categorical data** | Number and percentage (95% CIs) of participants. |
| | **Continuous data** | Mean and standard deviation, quartiles, minimum, and maximum. |
| **Transmissibility results** | **Categorical data** | Number and percentage (95% CIs) of participants. |
| **Vaccine virus stability** | **Categorical data** | Number and percentage (95% CIs) of participants. |
| **Immunogenicity results** | **Categorical data (cutoff)** | Number and percentage (95% CIs) of participants. |
| | **Continuous data (titer / data** | Log10: Mean and standard deviation.<br>Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum.<br>Graphical representation by Reverse Cumulative Distribution Curve (RCDC) |
| **Infectivity results** | **Categorical data** | Number and percentage (95% CIs) of participants. |
| **RSV WT infection** | **Categorical data** | Number and percentage (95% CIs) of participants, number of events, and 95% CI. |

The statistical methodology will be based on the use of two-sided 95% confidence intervals (CI).

All endpoints will be summarized by study intervention group. For the main parameters, 95% CI of point estimates will be calculated using the normal approximation for quantitative data and using the exact binomial distribution (Clopper-Pearson method) for proportions.

For immunogenicity data, assuming that Log10 transformation of the titers/titers ratio follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers/titers ratio) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in

order to provide geometric mean titers (GMTs) and geometric mean titers ratios (GMTRs) and their 95% CI.

GM is defined as follows: $GM = \left(\prod_{i=1}^{n} y_i\right)^{1/n} = 10\text{^}\left(\frac{1}{n}\sum_{i=1}^{n}\log_{10}(y_i)\right)$,

where $(y_1, y_2, \ldots, y_n)$ are the observed titers or individual ratios for each participant.

Viral shedding, vaccine virus stability (for pediatric participants receiving placebo and ad-hoc close contact participants), and safety analyses will be performed on the SafAS. Immunogenicity analyses and infectivity analyses will be presented on the FAS. Transmissibility analyses will be performed on the SafAS and PPAS as well as on other analysis set (ad-hoc close contact participants).

### 3.4.2 Primary Endpoints

#### 3.4.2.1 Vaccine virus transmission

Presence of vaccine virus detected by RSVt qRT-PCR (≥LOD) in nasal swabs after the first vaccination (D01, D04, D08, D11, D15, D18, and D22) will be summarized in pediatric participants receiving placebo with 95% CIs:

- Number and percentage of participants with vaccine virus detected at each timepoint
- Number and percentage of participants with vaccine virus detected in at least one nasal swab

Transmissibility analyses will be performed on the SafAS and PPAS. Vaccine virus transmission is defined in Section 4.2.1.

#### 3.4.2.2 Vaccine virus shedding

Titer of vaccine virus shedding evaluated by RSVt qRT-PCR in nasal swabs after each vaccination will be summarized at each timepoint (D01, D04, D08, D11, D15, D18, D22, D64, and D71) in pediatric participants by study intervention group with 95% CIs:

- Number and percentage of participants with detected shedding (≥LOD) at each timepoint
- Number and percentage of participants with quantified shedding (≥LLOQ) at each timepoint

In addition, titer of vaccine virus shedding will be summarized using descriptive statistics as presented in Table 3.1.

Viral shedding analyses will be performed on the SafAS.

#### 3.4.2.3 Vaccine virus stability

Presence of any vaccine virus variation will be described in pediatric participants receiving placebo and ad-hoc close contact participants:

- Number and percentage of participants with any variation in genetic sequence of ΔNS2, Δ1313, and I1314L segment of the vaccine virus compared to the reference strain vaccine virus isolates in the nasal swabs with detected vaccine virus (vaccine virus shedding by qRT-PCR ≥LOD).

Vaccine virus stability analysis will be performed on the SafAS .

The vaccine virus stability will be described as well in a random subset of pediatric participants receiving RSVt vaccine based on SafAS.

In order to organize the segment sequencing, a listing of samples to be sequenced is to be provided to the laboratory. The laboratory personnel must remain blinded therefore there should be no mention of the vaccine group in this listing. The nasal swab samples to be tested will be selected as follows:

- Any nasal swab with detected vaccine virus from a participant who received placebo at the previous vaccination and from ad-hoc close contact participants.
- The latest post-vaccination 1 nasal swab with detected vaccine virus among a subset (selected randomly) of 20 participants who received RSVt vaccine at the 1st vaccination and with detected vaccine virus in at least 1 nasal swab.
  Note: a subset of 10 participants randomly selected as defined above among the participants involved in the first interim analysis will be part of the first interim analysis
- The latest post-vaccination 2 nasal swab with detected vaccine virus in any participants who received RSVt vaccine at the 2nd vaccination and with detected vaccine virus in at least 1 nasal swab.

### 3.4.3 Secondary Endpoints

#### 3.4.3.1 Immunogenicity

RSV A serum neutralizing antibody titers and RSV serum anti-F IgG antibody titers will be summarized at each timepoint (D01, D57, and D85) in pediatric participants by study intervention group, including but not limited to:

- GMTs and 95% CI
- Geometric mean titers ratio (GMTR) relative to pre-vaccination titer and 95% CI.
- Number and percentage of participants with pre-vaccination titers < LLOQ or ≥ LLOQ
- Number and percentage of participants with post-vaccination titer ≥ 2-fold rise or 4-fold rise
- Reverse cumulative distribution curves (RCDCs)

Immunogenicity analyses will be presented on the FAS.

### 3.4.3.2 Safety

The following safety parameters will be described after each and any vaccination in pediatric participants by study intervention group with the 95% CIs of point estimates. SafAS will be used for analysis.

***Solicited Reactions***

Number and percentage of participants with:

- Presence of solicited administration site reactions and systemic reactions occurring up to 21 days after each and any vaccination
- Each solicited reaction according to time of onset, maximum intensity, and number of days of occurrence and action taken
- Any solicited reaction leading to study discontinuation

***Unsolicited Events and Reactions***

Number and percentage of participants with:

- Any unsolicited immediate systemic event in the 30 minutes after any vaccination according to System Organ Classes (SOC) and Preferred Terms (PT)
- Any unsolicited event and reaction 28 days after each and any vaccination according to SOC and PT
- Any unsolicited event/reaction according to time of onset, maximum intensity, and duration
- Any unsolicited event/reaction leading to study discontinuation

***AESIs***

Number and percentage of participants with:

- Any AESI within 28 days after each and any vaccination according to SOC and PT

***MAAEs***

Number and percentage of participants with:

- Any MAAEs within 28 days after each and any vaccination according to SOC and PT

***SAEs***

Number and percentage of participants with:

- Any SAE within 28 days after any vaccination according to SOC and PT, seriousness, and outcome
- Any SAE throughout the entire study according to SOC and PT, seriousness, and outcome

#### 3.4.3.3 Vaccine virus transmission

Presence of vaccine virus detected by RSVt qRT-PCR in nasal swabs after the second vaccination (D64 and D71) will be summarized in pediatric participants receiving placebo with 95% CIs:

- Number and percentage of participants with vaccine virus detected at each timepoint
- Number and percentage of participants with vaccine virus detected in at least one nasal swab

Transmissibility analyses will be performed on the SafAS. Vaccine virus transmission is defined in Section 4.2.1.

### 3.4.4 Exploratory Endpoints

#### 3.4.4.1 [redacted]

[redacted]

#### 3.4.4.2 [redacted]

[redacted]

#### 3.4.4.3 [redacted]

[redacted]

[redacted]

[redacted]

#### 3.4.4.4 [redacted]

[redacted]

### 3.4.5 Other Analyses

In addition to the analysis above, subgroup analyses for vaccine virus transmission, shedding and stability would be performed by age group (<12 months, ≥ 12 months).

As exploratory analysis, probability of transmission of vaccine virus would be calculated for the pediatric participants using Greenwood / Reed-Frost models after each administration of study intervention. Further details are provided in Appendix 2.

### 3.4.6 Handling of Missing Data and Outliers

#### 3.4.6.1 Safety

In all participant listings, partial and missing data will be clearly indicated as missing. No search for outliers will be performed.

##### 3.4.6.1.1 Immediate

For unsolicited systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

#### 3.4.6.1.2 Causal Relationship

By convention, all events reported at the administration site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the eCRF are also considered as related to vaccination and will be considered as reactions.

For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.

The missing relationship to study procedures for SAEs will not be imputed.

#### 3.4.6.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.4.1.1 For unsolicited AEs, missing intensities will remain missing and will not be imputed.

#### 3.4.6.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the Section 4.2.4.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

#### 3.4.6.1.5 Action Taken

Missing actions taken will remain missing and will not be imputed.

### 3.4.6.2 Immunogenicity/viral shedding

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.6.1.

### 3.4.6.3 Efficacy

No efficacy.

## 3.5 Interim Analyses

- An unblinded interim analysis will be performed on available data collected from D01 (V01) to D22 (V07) for participants randomized on or before 21July2023, in two steps:
    - The first step will be performed on available shedding / transmission data by RSVt qRT-PCR assay up to 21 days after the first study intervention administration, that will also include baseline immunogenicity data, safety data up to 21 days after the first study intervention administration, in order to share preliminary data to Health Authorities before moving to phase III clinical development. Randomization code will be broken for the Sponsor but blinding will be maintained at sites and participants/parents levels. Some listings will be generated to define the next steps for nasal swab testing (sequencing, plaque assay and WT RT-PCR).
    - The second step will be performed when subsequent data up to 21 days after the first study intervention administration will be available (e.g. segment sequencing, plaque assay and WT RT-PCR data).
- An additional unblinded interim analysis will be performed once all data collected from D01 (V01) to D22 (V07) from all participants is available. A two-step process of analysis will also be applied.
- The final unblinded statistical analysis will address the objectives on all participants

No statistical adjustment is necessary because no hypotheses will be tested.

This study will not include an early safety data review.

## 3.6 Data Monitoring Committee (DMC)

No DMC will be established.

# 4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

## 4.1 Complementary Information for Endpoints Assessment Methods

### 4.1.1 Primary Endpoints and Assessment Methods

#### 4.1.1.1 Transmission

See section 8.1.2 and section 9.3.2 of the protocol

#### 4.1.1.2 Vaccine virus shedding

See section 8.1.2 and section 9.3.2 of the protocol

#### 4.1.1.3 Stability

See section 8.1.2 and section 9.3.2 of the protocol

### 4.1.2 Secondary Endpoints and Assessment Methods

#### 4.1.2.1 Immunogennicity

See section 8.1.3 and section 9.3.3 of the protocol

#### 4.1.2.2 Safety

See section 8.2 and section 9.3.3 of the protocol

#### 4.1.2.3 Transmission

See section 8.1.2 and section 9.3.3 of the protocol

### 4.1.3 Exploratory Endpoints and Assessment Methods

#### 4.1.3.1 [redacted]

[redacted]

#### 4.1.3.2 [redacted]

[redacted]

#### 4.1.3.3 [redacted]

[redacted]

### 4.1.4 Safety Exploratory Endpoints and Assessment Methods

No safety Exploratory Endpoints

## 4.2 Complementary Information on Derived Endpoints: Calculation Methods

### 4.2.1 Vaccine Virus Transmission

Vaccine virus transmission is defined as presence of detected vaccine virus confirmed by RSVt qRT-PCR assay (vaccine virus shedding ≥ LOD) in pediatric participants receiving placebo and ad-hoc close contact participants.

Detected viable RSV virus is defined as values from the plaque assay ≥ LOD.

### 4.2.2 Vaccine virus shedding

Detected virus shedding is defined as vaccine virus shedding ≥ LOD by RSVt qRT-PCR assay.

Quantified virus shedding is defined as vaccine virus shedding ≥ LLOQ by RSVt qRT-PCR assay.

### 4.2.3 Infectivity

Infectivity is defined as detection of vaccine virus strain in any post-vaccination nasal swab sample by RSVt qRT-PCR and/or a >= 4-fold rise from baseline (D01) in RSV A serum nAb titers and/or RSV serum anti-F IgG Ab titers.

- Infectivity after vaccination 1: Detection of vaccine virus shedding (≥LOD) by RSVt qRT-PCR at any post-vaccination 1 NS samples (D04, D08, D11, D15, D18 and D22) and/or a >= 4-fold rise from baseline (D01) in RSV A serum nAb titers and/or RSV serum anti-F IgG Ab titers at D57
- Infectivity after vaccination 2: Detection of vaccine virus shedding (≥LOD) by RSVt qRT-PCR at any post-vaccination 2 NS samples (D64 and D71) and/or a >= 4-fold rise from baseline (D01) in RSV A serum nAb titers and/or RSV serum anti-F IgG Ab titers at D85
- Infectivity after any vaccination: Detection of vaccine virus shedding (≥LOD) by RSVt qRT-PCR at any post vaccination NS samples (D04, D08, D11, D15, D18, D22, D64 and D71) and/or a >= 4-fold rise from baseline (D01) in RSV A serum nAb titers and/or RSV serum anti-F IgG Ab titers at D57 and /or D85

### 4.2.4 Safety

#### 4.2.4.1 Solicited Reactions

##### 4.2.4.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3 or Missing for solicited administration site reactions; and None, Grade 1, Grade 2, Grade 3, or Missing for solicited systemic reactions.

For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database and grade reported as "unknown" will be considered as "Missing". When in the CRF presence is recorded as "No" and with all daily records missing then all daily intensities will be derived as "None".

For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the Section 10.2.5 of the protocol. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator.

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

##### 4.2.4.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.4.1.1 and is calculated as the maximum of the daily intensities over the period considered.

##### 4.2.4.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

- None: No presence
- Grade 1, Grade 2, Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as D01-D04, D05-D08, D09-D15, D16-D22, D23 or later.

##### 4.2.4.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.4.1.1. It corresponds to the first day with intensity of Grade ≥1.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Time of onset period is displayed as D01-D04, D05-D08, D09-D15, D16-D22

#### 4.2.4.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.2.4.1.1. It corresponds to the number of days with daily intensities of Grade ≥1. Number of days of presence on the solicited period with a specified intensity may also be derived.

Number of days of presence during the solicited period is displayed as 1-3 days, 4-7 days, 8-14 days, 15-21 days, 22 days.

#### 4.2.4.1.6 Overall Number of Days of Occurrence/ Presence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

- (end date – last vaccination date) + (number of days of presence within the solicited period) – length of the solicited period + 1

If the end date is missing or incomplete (contains missing data [MD]), the overall number of days of presence will be considered as Missing.

Overall number of days of presence is displayed as 2-3 days, 4-7 days, 8-14 days, 15-21 days, 22 days or more, and Missing end date.

#### 4.2.4.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.4.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction. Note the intensity could be considered None (not a reaction) in the analysis despite being considered a reaction by the investigator.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

#### 4.2.4.2 Unsolicited AEs

##### 4.2.4.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

##### 4.2.4.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in Table 10.1 and 10.2 of the protocol for that measurable solicited reaction. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator.

Intensity for the other unsolicited AEs will correspond to the value reported in the eCRF.

The maximum intensity corresponds to the highest intensity for a unique term.

##### 4.2.4.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the eCRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE

If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE

##### 4.2.4.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.2.4.2.3:

- start date of the unsolicited AE – date of last vaccination before the unsolicited AE

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "within 28 days" after each vaccination (i.e. acute phase), which corresponds to AEs with a time of onset between D01 and D29 days. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.2.4.2.3), so will be included in these tables.

Time of onset period is displayed as D01-D04, D05-D08, D09-D15, D16 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately

#### 4.2.4.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

- end date of unsolicited AE – start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

Duration period is displayed as 1-3 days, 4-7 days, 8-14 days, 15 or more, and Missing

#### 4.2.4.2.6 Medically-Attended Adverse Event

An event will be considered as an MAAE if "Yes" is checked for "Is the event an MAAE?" in the eCRF.

#### 4.2.4.2.7 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the eCRF.

SAEs will be analyzed throughout the study using the following periods:

- Within 28 days after any vaccination
- During the study (i.e., all SAEs occurred during the study)

#### 4.2.4.2.8 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the eCRF.

The following AESIs will be assessed during the Acute Phases of the study:

[redacted]

[redacted]

### 4.2.4.3 Solicited and Unsolicited AEs after any vaccination

This section is applicable for tables which present results after any vaccination.

The rules for calculation are to select the worst case:

- Maximum intensity: Select the maximum overall intensity for any vaccination
- Time of onset: Select the minimum time of onset for any vaccination
- Duration (for unsolicited AE): Select the maximum duration for any vaccination

### 4.2.5 Other Safety Endpoints

#### 4.2.5.1 Pregnancy

Not applicable as women of childbearing age will not receive the study intervention.

#### 4.2.5.2 Action Taken

Missing actions taken will remain missing and will not be imputed

#### 4.2.5.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

#### 4.2.5.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

#### 4.2.5.5 Causal Relationship

This information will be summarized as collected in the field “Relationship to study vaccine”. Missing causal relationship will be handled as described in 3.4.6.1.2. Relationship to study procedure is only presented in the listing.

#### 4.2.5.6 Adverse Events Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to study discontinuation.

The items that are counted are:

- Disposition table: A subject who, on the “Completion at End of Study” form question “What was the subject's status?” has “Adverse Event” checked.
- Safety overview table: A participant who has either on the “Completion at End of Study” form question “What was the subject’s status?” has “Adverse Event” checked, or lists a solicited AE that has “Caused Study Termination” checked that is at least Grade 1 or an unsolicited AE that has “Caused Study Discontinuation” checked that is at least Grade 1 or missing and is within the time period indicated.
- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has “Caused Study Termination” checked that is at least Grade 1 or an unsolicited AE that has “Caused Study Discontinuation” checked that is at least Grade 1 or missing and is within the time period indicated.

### 4.2.6 Immunogenicity

#### 4.2.6.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantification [LLOQ] and ≥ upper limit of quantification [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

For the RSV serum anti-F IgA antibodies, we will consider the LOD value for the calculation instead of the LLOQ.

Note for titers converted into IU/mL:

The IU/mL is computed using the following calibration formulae:

$$\text{IU/mL} = \frac{Sample\ Titer}{(Assay\ calibrator)/Assigned\ Potency} = \frac{Sample\ Titer}{(Assay\ calibrator)/Assigned\ Potency}$$

Where:

- *Sample Titer*: This is the titer directly observed from the sample using one plate.
- *Assigned Potency*: The established internal reference standard and replacement for International
- *Assay calibrator*: Each plate will also measure the titer of the reference standard

Because of this calibration formula, LLOQ related to titers can be calibrated to different IU/mL depending on the observed titer of calibrator (international reference or in-house reference); so titer < LLOQ is not consistent converting to IU/mL from run to run.

As a consequence, for any value reported as "< X", we use the computed value X/2. No ULOQ is defined.

#### 4.2.6.2 Fold-rise

For calculation of fold-rise and geometric mean titer ratio (GMTR) a titer reported as < LLOQ will be converted to ½ LLOQ for a numerator and will be converted to LLOQ for a denominator. If both numerator and denominator are < LLOQ, then both will be converted in the same way so that titer ratio=1. This rule is used to minimize the numerator and maximize the denominator as a conservative approach. For the RSV serum anti-F IgA antibodies, we will consider the LOD value for the calculation instead of the LLOQ.

Note for titers converted into IU/mL: This rule would apply using X instead of LLOQ

If the computed value is ≥ 4-fold rise, then the derived ≥ 4-fold rise indicator will be "Yes" for that test, otherwise ≥ 4-fold rises will be "No".

Note: If either numerator or denominator is missing, then fold-rise computed value/indicator is missing.

#### 4.2.6.3 Baseline RSV serostatus

For this Sanofi Phase II study, baseline RSV serostatus will be determined from serum samples collected at baseline (V01). Participants will be categorized into RSV-exposed or RSV-naïve based on the presence or absence of detectable serum anti-F IgA antibodies. This biomarker has been chosen since it is produced only in response to RSV infection and not transferred trans-placentally from mother to child. Baseline serostatus will be determined as follows:

- ***RSV-naive*** for participants with baseline IgA titer < LOD
- ***RSV-exposed*** for participants with baseline IgA titer ≥ LOD
- ***Undetermined*** for participants with baseline IgA titer 'missing' or 'NR'.

### 4.2.7 [redacted]

#### 4.2.7.1 [redacted]

### 4.2.8 Derived Other Variables

#### 4.2.8.1 Age for Demographics

Calendar age (in months) calculated using date of birth collected at time of visit 01 will be used in the analysis.

Following age groups will be derived, corresponding to stratification factor:

- < 12 months: until the last day before the 1st birthday date
- ≥ 12 months: from 1st birthday date

#### 4.2.8.2 Duration of a Participation in the Study

The duration of a participation in the study is computed in days as follows: maximum (date of visit, date of termination form, 6-month follow-up contact) - date of visit 01 +1.

#### 4.2.8.3 Duration of the Study

The duration of the study is computed in days as follows: maximum of all participants (date of visit, date of termination form, 6-month follow-up contact) - minimum for all participants (date of visit 01) +1.

#### 4.2.8.4 Duration of a Participation in the Study Intervention Phase

The duration of a participation in the study is computed in days as follows: maximum (date of visit, date of termination form) - date of visit 01 +1.

#### 4.2.8.5 Duration of the Study Intervention Phase

The duration of the study is computed in days as follows: maximum of all participants (date of visit, date of termination form) - minimum for all participants (date of visit 01) +1.

# 5 Changes in the Conduct of the Trial or Planned Analyses

Not applicable

# 6 Supporting Documentation

## 6.1 Appendix 1 List of Abbreviations

| | |
|---|---|
| AE | Adverse Events |
| AESI | Adverse events of special interest |
| AR | Adverse reactions |
| ARI | Acute respiratory illness |
| CRF | Case report form |
| DMC | Data Monitoring Committee |
| ELISA | Enzyme-linked Immuno-adsorbant Assay |
| FAS | Full analysis set |
| GCI | Global Clinical Immunology |
| GCP | Good Clinical Practice |
| GM | Geometric mean |
| GMT | Geometric mean of titer |
| GMC | Geometric mean of concentration |
| ICH | International Council for Harmonisation |
| IMP | Investigational Medicinal Product |
| LAR | Legally acceptable representative |
| LRI | Lower respiratory tract illness |
| LOD | Limit of detection |
| LLOQ | Lower level of quantitation |
| MAAE | Medically attended adverse event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NA | Not applicable |
| NC | Not computed |
| NIMP | Non- Investigational Medicinal Product |
| PPAS | Per-protocol analysis set |
| RCDC | Reverse cumulative distribution curve |
| RSV | Respiratory Syncytial Virus |
| SAE | Serious adverse events |
| SafAS | Safety analysis set |

| | |
|---|---|
| SAP | Statistical analysis plan |
| SOC | (Primary) System organ class |
| PT | Preferred term |
| TLF | Tables, listings and figures |
| ULOQ | Upper level of quantitation |
| URI | Upper respiratory tract illness |

## 6.2 Appendix 2 Use the Reed-Frost models and Greenwood models to estimate the transmission probability.

The binomial model is often used to estimate the transmission probability based on the idea that exposure to infection occurs in discrete contacts. Generally, p is defined as the transmission probability during a contact between a susceptible person and an infectious person. The quantity $q = 1 - p$ is the probability that the susceptible person will not be infected during the contact, called the escape probability. In this section, the susceptible person is considered the pediatric participant who received placebo, and an infectious person is considered the pediatric participant who received RSVt vaccine.

Chain binomial models are dynamic models developed from the simple binomial model by assuming that infection spreads from individual to individual in populations in discrete units of time, producing chains of infection governed by the binomial probability distribution. The Reed-Frost and Greenwood models are examples of chain binomial models. To use these models, the number of susceptible persons and the number of infectious persons involved in each transmission generation should be known. However, in this study, the actual transmission chains is not observed, thus a single transmission generation is considered.

A contact group is defined as a group of pediatric participants who live in the same household or who attend in the same daycare center. A contact group is considered as a transmission unit and different contact groups are assumed to be separate and independent of one another. A total of *J* contact groups is assumed. $S_j$ and $I_j$ are the number of pediatric participants who received placebo and the number of pediatric participants who received RSVt vaccine in the *j*th contact group, respectively. $X_j$ is the total number of pediatric participants who received placebo and have detective vaccine virus in the *j*th contact group.

***Reed-Frost models***

The Reed-Frost model assumes that exposure to two or more infectious people at the same time are independent exposures.

Suppose a contact group with five pediatrics, where two received placebo and three received RSVt vaccine. The probability that a pediatrics who received placebo escape transmission from all the three pediatrics who received RSVt vaccine is calculated as $q^3$ , so the probability of getting transmitted is $1 - q^3$ . The probability that all two placebo-pediatrics escape transmission from all three pediatrics who received RSVt vaccine is $q^{3*2}$ . Similarly, the probability that all the two placebo-pediatrics get transmitted is $(1 - q^3)^2$.

Then based on the Reed-Frost model, the likelihood function for estimating $p$ is

$$L(p) = \prod_{j=1}^{J} \binom{S_j}{X_j} (1 - q^{I_j})^{X_j} q^{I_j(S_j - X_j)}$$

The log likelihood is,

$$logL(p) = \sum_{j=1}^{J} \log(\frac{S_j!}{S_j!\,(S_j! - X_j!)}) + \sum_{j=1}^{J} X_j \log(1 - q^{\,I_j}) + \log(q) \sum_{j=1}^{J} (S_j - X_j) I_j$$

***Greenwood models***

The Greenwood model assumes that exposure to two or more infectious people at the same time is equivalent to exposure to one. That is, the probability of becoming transmitted from exposure to one or more vaccinees is still $p$. Then the likelihood function for estimating $p$ is

$$L(p) = \prod_{j=1}^{J} \binom{S_j}{X_j} p^{X_j}\, q^{(S_j - X_j)}$$

The log likelihood is,

$$logL(p) = \sum_{j=1}^{J} \log(\frac{S_j!}{S_j!\,(S_j! - X_j!)}) + \log(p) \sum_{j=1}^{J} X_j + \log(q) \sum_{j=1}^{J} (S_j - X_j)$$

***Maximum Likelihood Estimation***

The maximum likelihood is used for parameter estimation. The basic idea behind maximum likelihood estimation is to find the value $\hat{p}$ which is most likely to have produced the data. The statistic $\hat{p}$, if it exists, is called the maximum likelihood estimate of $p$. Maximizing $L(p)$, the probability of observing the actual data, is equivalent to minimizing the negative log likelihood, -*log*(*L*).

SAS/IML procedure is used to compute maximum likelihood estimate and the 95% confidence interval for $p$.

# 7 References

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