SAP Core Body

Title: A parallel group, Phase III, randomized, observer blind, placebo controlled, multi-center, multinational, multi-arm study to demonstrate non-inferiority of the immune response of a low dose compared to the standard dose and to evaluate the safety of a respiratory syncytial virus vaccine in infants and toddlers (OPAL)

Study Code: VAD00015

Study Phase: 3

SAP Core Body Version: 1.0

SAP Core Body Date: 09 FEB 2026

Protocol Version Number: 3.0

The SAP Code Body should be used in conjunction with the study protocol and the SAP TLF.

Version History

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

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1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the statistical methodologies and analyses to be conducted for the clinical study, in alignment with the study protocol. The SAP is intended to supplement and operationalize the statistical principles outlined in the study protocol, ensuring transparency, reproducibility, and regulatory compliance.

This document constitutes Version 1.0 of the SAP. Following review of the pre-planned Benefit Assessment (BA) as specified in the Independent Data Monitoring Committee (IDMC) SAP for VAD00004 study, the IDMC concluded that the RSVt vaccine did not demonstrate sufficient efficacy in preventing respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) and recommended to halt the trial. Based on this recommendation, the sponsor decided to discontinue the study. As a result, several analyses originally specified in the study protocol will not be performed, this will be summarized in section 6 of the SAP.

The reference protocol for this SAP Version 1.0 is Protocol Version 3.0, which was the final version submitted to and approved by the Ethics Committee (EC)

2. Overall Design

The design of the study is summarized in Table 2.1.

Table 2.1: Study design

Type of design	Parallel, multinational, multi-center
Phase	3
Control method	Placebo-controlled
Study population	Healthy infants and toddlers aged 6 months to < 22 months. **Cohort 1**: Participants born after a gestation period of 28 through 36 completed weeks and medically stable. **Cohort 2**: Participants born after a gestation period of ≥ 37 weeks. Contingent upon an acceptable safety profile of the HD in preterm participants, enrolment in Cohort 2 will proceed to include participants born preterm. Cohort 1 and Cohort 2 participants will be enrolled in parallel.
Regions	European Union, Latin America, and North America

Level and method of blinding	Observer-blind: • Blinding for vaccine group assignment: participants, parents or legally acceptable representative (LAR), outcome assessors, investigators, laboratory personnel, sponsor study staff* • No blinding for study staff who prepare and administer the study interventions *Generally, safety data review during the study will be performed in a blinded manner by the Sponsor Safety Management Team (SMT). Safety data for Cohort 1 participants will be reviewed in an unblinded manner at the predefined time-points, involving pause of enrollment.
Investigational intervention assignment method	**Cohort 1**: (1:1 randomization) Group 1 (N=10): 2 administrations of SD RSVt Group 2 (N=10): 2 administrations of placebo (2:1 randomization) Group 3 (N=10): 2 administrations of HD RSVt Group 4 (N=5): 2 administrations of placebo Group 1 and 2 participants will be enrolled first and will be randomized to receive either SD RSVt vaccine or placebo. Based on the acceptable safety profile up to 28 days after the first vaccination, enrolment of participants into Groups 3 and 4 will proceed. Respectively, enrollment of pre-term duration participants in Cohort 2 will initiate, based on the acceptable safety profile up to 28 days after the first vaccination of Groups 3 and 4. **Cohort 2 (2:2:2:1 randomization):** Group 1 (N=304): 2 administrations of LD RSVt Group 2 (N=304): 2 administrations of SD RSVt Group 3 (N=304): 2 administrations of HD RSVt Group 4 (N=152): 2 administrations of placebo Cohort 2 participants will be randomized to receive either LD, SD, or HD RSVt vaccine or placebo. Randomization will be stratified by study country, age group (< 12 months and ≥ 12 months), and potential RSV seropositivity (based on maternal immunization, and previous receipt of RSV mAb). Cohorts 1 and 2 will enroll in parallel.

Table 2.2: Schedule of activities for the Main Set of participants

Phase 3 Study, 5 Planned Visits, 3 Phone Calls, 2 Vaccinations, 2 Blood Samples, 2 Nasal Samples, approximately 8 Months' Duration Per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V01)**	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone Call**	**Phone Call**
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Informed consent	X	X							
Inclusion/exclusion criteria	X	X							
Collection of demographic data	X	X							
Collection of medical history (including participant past RSV illness, maternal RSV vaccination and RSV disease during pregnancy)	X Significant Medical History	X							
Physical examination		X			X				
Pre-vaccination temperature[1]		X			X				
Vital signs		X			X				
Collection of reportable concomitant medications/vaccinations (including participant RSV mAb receipt)	X	X	X	X	X	X	X		
Randomization/allocation of participant number	X	X							

[1] Axillary pre-vaccination body temperature will be collected during vaccination visits and reported in the source document.

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V01)**	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone Call**	**Phone Call**
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Dose number	X	X			X				
Blood sampling (BL) [5 mL]	X	**BL0001**					**BL0002**		
Nasal sample (NS)	X		**NS0001**			**NS0002**			
Vaccination (VAC)	X	**VAC1**			**VAC2**				
Immediate surveillance (30 min)[2]	X	X			X				
Participant diary or Memory Aid (MA) provided[3]		X			X		X		
Participant diary or MA reviewed[4]			X	X	X	X	X	X	X
Participant diary or MA collected (if applicable)					X		X		
Collection of solicited administration site and systemic reactions[5]	X	X	X		X	X			
Collection of unsolicited AEs[6]	X	X	X	X	X	X	X		
Collection of SAEs, AESIs, and MAAEs (throughout the study)	X	X	X	X	X	X	X	X	X

[2] Any unsolicited systemic adverse events occurring within the 30 minutes from study intervention administration will be recorded as immediate unsolicited systemic AE in the CRF.

[3] At each visit the investigator will remind the participants' parents/LARs to fill out the participant diary or MA if applicable and will answer any questions.

[4] At each phone call, the investigator will interview the participants' parents/LARs to review the information recorded in the participant diary or MA and will attempt to clarify anything that is incomplete or unclear. The paper participant diary will be collected and archived on site as described in the table.

[5] Solicited administration site and systemic reactions will be collected for 21 days after each vaccine administration.

[6] Unsolicited AEs will be collected for 28 days after each vaccine administration.

Visit/Contact	***Collection of information in the CRF***	**Visit 1 (V01)**	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone Call**	**Phone Call**
Study timelines - days(D)		D01	D08	D29	D57	D64	D85	D147	D237
Visit Interval (V0X + days)		NA	V01+7	V01+28	V01+56	V03+7	V03+28	V03+3 months	V03+6 months
Time windows (days)		NA	[+2]	[+2]	[+14]	[+2]	[+7]	[+14]	[+14]
Age (months)		**6 to < 22**			**8 to < 24**				
Collection of End of Study Intervention Phase status[7]	X						X		
Collection of 6-Month Follow-up - End of Study status[8]	X								X

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CRF, case report form; LAR, legally acceptable representatives; MA, memory aid; MAAE, medically attended adverse event; SAE, serious adverse event

[7] In case of participant discontinuation at a visit, all the CRF forms related to this visit will be completed with available information.

[8] A phone call will be made at least 6 months after the last study intervention received for all the participants, including early terminated participants.

Table 2.3: [redacted]

[redacted]

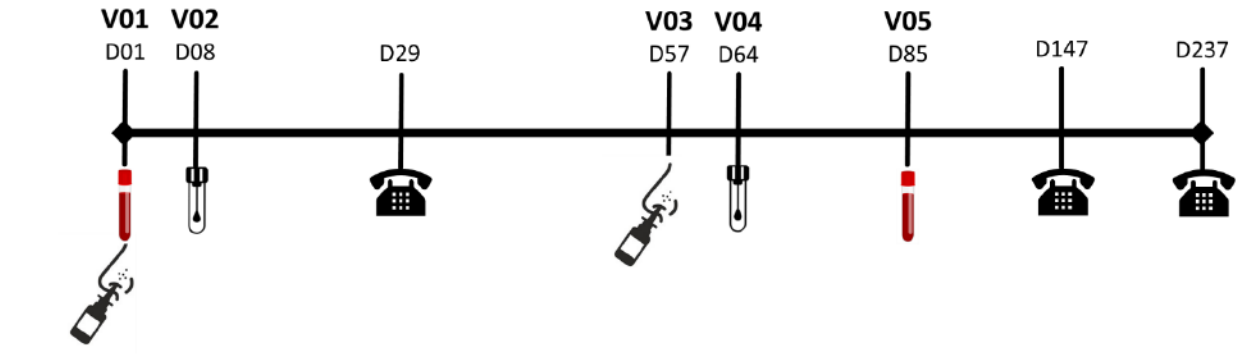
[redacted]



[15] In case of participant discontinuation at a visit, all the CRF forms related to this visit will be completed with available information.

[16] A phone call will be made at least 6 months after the last study intervention received for all the participants, including early terminated participants.

Figure 2.1: Graphical study design - Main set of participants



Legend:



Abbreviations: D=day; V=visit
RSVt vaccine (low-, standard-, or high-dose) or placebo to be administered intranasally at V01 and V03.
Blood samples will be collected at V01 (pre-vaccination) and V05 for immunogenicity assessments.
Nasal samples will be collected 7 days post vaccination at V02 and V04 for vaccine viral shedding determination.

Figure 2.2: [redacted]

[redacted]

3. Objectives and Endpoints

The study objectives, and the corresponding endpoints and estimands are described in Table 3.1.

Due to the halt of the study, data collected for the study will not permit us to complete objectives. Details are presented in the section 6 of this SAP.

Table 3.1: Objectives and corresponding endpoints and estimands

Objectives	Endpoints	Estimands and Estimators	
		Population-level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Primary			
Immunogenicity 1. To demonstrate the non-inferiority of 2 administrations of the LD RSVt vaccine antibody levels to RSV A and RSV B compared to the SD RSVt vaccine (Cohort 2)	• RSV A and RSV B serum neutralizing antibody titers at 28 days post-dose 2 (D85)	Ratio of GMTs between groups (LD RSVt / SD RSVt) of each RSV antibody (A and B) Success criteria: The non-inferiority of LD RSVt versus SD RSVt will be demonstrated if the lower limit (LL) of the 2-sided 95% CI of the ratio of GMTs is > 2/3 for both RSV antibodies (A and B)	Immunogenicity will be estimated in the setting where participants do receive the full vaccination schedule and do not deviate from protocol requirements potentially impacting immunogenicity, as defined in the Per-Protocol Analysis set* (PPAS) Other intercurrent events will be handled as per Treatment Policy Strategy. Missing data will not be imputed unless specified in the SAP.

Objectives	Endpoints	Estimands and Estimators	
		Population-level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Safety 2. To assess the safety profile of the SD and HD RSVt vaccine after each and any administration in medically stable participants born preterm (Cohort 1) 3. To assess the safety profile of the LD/SD/HD RSVt vaccine after each and any administration in Cohort 2 participants	• Presence of unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited administration site reactions within 21 days after each vaccination • Presence of solicited systemic reactions within 21 days after each vaccination • Presence of unsolicited AEs within 28 days after each vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study	The main parameters for the safety endpoints will be described by number of participants, percentage, and 95% CI using the exact binomial distribution (Clopper Pearson method) for single proportion.	Safety will be estimated in the setting where participants received at least one study intervention administration as defined in the Safety Analysis Set**. Any relevant intercurrent event will be handled according to treatment policy strategy. Missing data will not be imputed unless specified in the SAP.
Secondary			
Immunogenicity 4. To describe the RSVt vaccine humoral immune responses in Cohort 1 participants 5. To describe the RSVt vaccine humoral immune responses in Cohort 2 participants	• RSV A and RSV B serum neutralizing antibody titers at baseline (D01) and D85 • RSV serum anti-F IgA and anti-F IgG antibody titers at D01 and D85		

Objectives	Endpoints	Estimands and Estimators	
		Population-level summary	**Data handling strategy** (Analysis set, Intercurrent events, Missing data)
Vaccine Virus Shedding 6. To describe the vaccine virus shedding in all participants with detected vaccine virus after each administration (Cohort 1 and Cohort 2)	• Presence of RSVt vaccine virus viral shedding in D08 and D64 nasal samples measured by qRT PCR • Titer of vaccine virus shedding in D08 and D64 nasal samples quantified by qRT-PCR		
Exploratory			
[redacted]			

Preterm=born after a gestation period of 28 through 36 weeks. At term= born after a gestation period of ≥ 37 weeks.
LD=target [redacted] PFU; SD=target [redacted] PFU; HD=target [redacted] PFU
Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; D, day; GMTs, geometric mean titers HD, high dose; LD, low dose; LL, lower limit; MAAE, medically attended adverse event; PFU, plaque forming units; qRT-PCR, quantitative real time-polymerase chain reaction; SAE, serious adverse event; SD, standard dose; RSV, respiratory syncytial virus.
*The primary population of interest for immunogenicity is defined as participants meeting the inclusion and exclusion criteria at the time of enrollment, receiving full vaccination schedule, and not deviating from protocol requirements potentially impacting immunogenicity.
**The primary population of interest for safety is defined as participants receiving at least one dose of study vaccine.

4. Statistical Considerations

4.1 Statistical Hypotheses

Due to the halt of the study, participants did not receive second administration, no immunogenicity results will be available 28 days after second administration. Section 4.1.1 and 4.1.2 of this SAP are not applicable (cf section 6).

4.1.1 Immunogenicity

Twenty-eight days after the second administration of the RSVt vaccine to participants in Cohort 2, the geometric mean titers (GMTs) of neutralizing RSV (A and B) antibodies of the LD RSVt group will be compared to SD RSVt group. The following hypotheses will be tested for each anti-RSV neutralizing antibody:

$$H_0 : \text{GMT(rsv, LD)/GMT(rsv, SD)} \leq 2/3$$
$$H_1 : \text{GMT(rsv, LD)/GMT(rsv, SD)} > 2/3$$

where GMT(rsv, LD) and GMT(rsv, SD) are GMTs of RSV antibodies (A and B) in LD RSVt and SD RSVt from Cohort 2, respectively.

If the lower limit of the 2-sided 95% CI of the ratio of the GMTs between LD RSVt and SD RSVt groups is > 2/3 for both neutralizing RSV antibodies (A and B), the inferiority null-hypothesis will be rejected and non-inferiority (NI) of LD RSVt compared to SD RSVt will be demonstrated.

4.1.2 Multiplicity Adjustment

Each of the anti-RSV antibodies (A and B) will be tested separately for primary immunogenicity objective. No multiplicity adjustment will be performed

4.2 Sample Size Determination



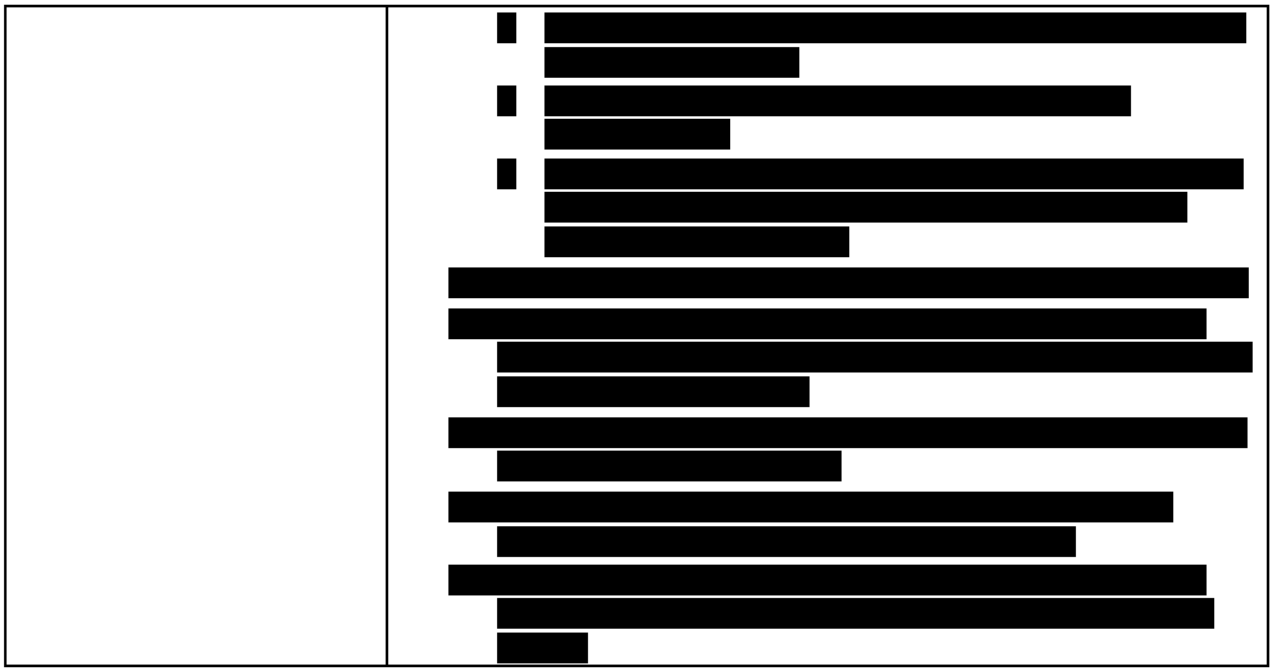
Table 4.1: [redacted]

[redacted]

4.3 Populations for Analyses

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

Participant Analysis Set	Description
Randomized	Participants for whom a study intervention group has been allocated.
Safety Analysis Set (SafAS)	Participants who have received at least one administration of the study intervention. All participants will have their safety analyzed after each administration according to the study intervention they actually received, and after any vaccination according to the study intervention received at the 1st administration of the study intervention. 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 participants who received at least 1 administration of the study intervention. Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: [redacted]



4.4 Statistical Analyses

4.4.1 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 4.2: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	Number and percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Baseline characteristics	**Categorical data**	Number and percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs for main endpoints) of participants. Unsolicited: Number and percentage (95% CIs) of participants and number of events.
Immunogenicity results	**Categorical data**	Number and percentage (95% CI) of participants.
	Continuous data (titer / data†)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum.

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), i.e., using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a

[redacted]

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

As mentioned in the study protocol, the immunogenicity analyses on primary endpoints was supposed to be performed on the PPAS and confirmed on the FAS. For other immunogenicity endpoints, analyses was supposed to be performed on the PPAS and confirmed on the FAS if the difference between number of participants in the PPAS and the number of participants in the FAS is not less than 10%.

Due to the stop of the study, it was decided to only perform analysis on the FAS (cf section 6).

Vaccine virus shedding and safety analyses will be performed on the Safety Analysis Set (SafAS).

4.4.2 Primary Endpoints

Immunogenicity

Due to the stop of the study, the non-inferiority analysis initially scheduled in the protocol will not be performed (cf section 6).

Safety

Due to the halt of the study, no participants received vaccination 2. Only safety after vaccination 1 and during the study will be presented. Safety results will be described by study intervention group. The safety analyses will be performed on the SafAS.

Solicited adverse reactions (ARs), unsolicited AEs, SAEs, MAAEs and AESIs will be summarized. The main parameters will be described by study intervention group after each and any study intervention administration with the 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions. Overview of the safety data will be presented, including the following parameters

- Unsolicited systemic AEs occurring within 30 minutes of administration (immediate unsolicited AEs)
- Solicited administration site reactions and solicited systemic reactions within 21 days after first administration.
- Unsolicited AEs occurring within 28 days after first administration by system organ class (SOC) and preferred term (PT)

- All SAEs that occur within 28 days after first administration and throughout the study
- All MAAEs and AESIs that occur within 28 days after first administration and throughout the study

Listings will be used to present details of each parameter:

- For solicited reaction: occurrence, time to onset, intensity, number of days of occurrence, action taken, and whether the reaction led to early termination from the study
- For unsolicited AE, MAAE and AESI: relationship, intensity, time to onset, duration and whether the AE led to early termination from the study
- For SAE: after each / any administration by SOC and PT, seriousness criteria, time to onset, outcome, relationship, and whether the SAE led to early termination

4.4.3 Secondary Endpoints

Immunogenicity

Distribution of baseline serostatus (D01) will be described with 95% CIs.

The 95% CIs for the Geometric Mean Titers (GMTs) will be calculated using a normal approximation of log10-transformed titers.

The 95% CIs for the proportions will be based on the Clopper-Pearson method.

Vaccine Virus Shedding

Presence of vaccine virus detected in D08 nasal samples and titer distribution of vaccine virus shedding, will be summarized for all participants by study intervention group with 95% CIs.

4.4.4 Exploratory Endpoints

[redacted]

4.4.5 Other Analyses

Vaccine virus shedding after vaccination 1 will be described by baseline serostatus.

4.4.6 Handling of Missing Data and Outliers

4.4.6.1 Safety

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

4.4.6.1.1 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 (ie, will not be considered as "Immediate").

4.4.6.1.2 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 electronic case report (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 (ie, will not be considered as "Related")

4.4.6.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 5.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

4.4.6.1.4 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 within or not within the defined time window as described in Section 5.2.1.2.4, according to the last vaccination (computed according to the Section 5.2.1.2.3). 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.

4.4.6.1.5 Action Taken

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

4.4.6.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. Lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ) management will be performed as described in Section 5.2.2.1.

4.4.6.3 Imputation Rules for Missing Dates of Concomitant Medications

Incomplete Start Dates

When incomplete start dates (i.e., with missing day, month, or year) are used in calculations, the following rules will be applied:

- **If only the day is missing**, use the first day of the month, unless:
  - The start month and year of the medication/vaccination coincide with the month and year of one of the study intervention administrations AND the medication/vaccination end date is on or after the date of one of the study intervention administrations, or the end date is missing/partially undetermined. In this case, the date of the study intervention administration that coincides with the start month and year of the medication/vaccination will be used.
- **If both the day and month are missing**, use the first day of the year, unless:
  - The start year of the medication/vaccination coincides with the start year of one of the study intervention administrations AND the medication/vaccination end date is on or after the date of one of the study intervention administrations, or the end date is missing/partially undetermined. In this case, the date of the study intervention administration that coincides with the start year of the medication/vaccination will be used.
- **If the day, month, and year are all missing**, attempt to query to obtain the date. If not possible, use the earliest date of study intervention administration, unless:

The medication/vaccination end date is before the earliest date of study intervention administration. In this case, the first day of the month of the medication/vaccination end date will be used if the medication/vaccination end date is known to the month level. If the medication/vaccination end date is only available at the year level, the first day of that year will be used

4.5 Sequence of Analyses

In the context of halting the trial prematurely, a final analysis will be conducted after the official final DataBase Lock of the study.

4.6 Data Monitoring Committee (DMC) and Safety Management Team (SMT)

An IDMC (Independent Data Monitoring Committee) will be appointed for this study. The IDMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for harms or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter..

Participant safety will also be continuously monitored by the Sponsor's internal safety management team (SMT), which includes safety signal detection at any time during the study.

This committee, led by the Patient Safety and Pharmacovigilance (PSPV) representative and the Responsible Medical Officer (RMO), will be responsible for the review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

5. 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.

5.1 Complementary Information for Endpoint Assessment Method

Not Applicable

5.2 Complementary Information on Derived Endpoints: Calculation Methods

5.2.1 Safety

5.2.1.1 Solicited Reactions

5.2.1.1.1 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 (Unknown).

To derive daily intensity of solicited reactions, the sequential steps will be applied as follows:

For non-measurable solicited reactions, daily intensity will correspond to daily records as reported in the clinical database.

For measurable solicited reactions, the daily measurements reported in the clinical database will be converted according to the intensity scales defined in the protocol.

In case of daily intensity assessments between the investigator and the participant are different, the investigator's assessment available for any given days will be used for those days. Otherwise, the participant's assessment will be used for any given days in which the investigator's assessment is not available.

5.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 5.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

5.2.1.1.3 Presence

Presence is derived from the maximum overall intensity in 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

5.2.1.1.4 Time of Onset

Time of onset is derived from the computed daily intensity as described in Section 5.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3. In case of any missing intensity before this day, the time of onset is missing. If a reaction is not continuous (ie, a reaction occurs over 2 separate time periods intervened by at least 1 daily intensity of None or Missing), then the time of onset is the first day of the first presence.

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

5.2.1.1.5 Number of Days of Presence

Number of days of presence over the period considered is derived from the computed daily intensity as described in Section 5.2.1.1.1. It corresponds to the number of days with a daily intensity of Grade 1, Grade 2, or Grade 3. Number of days of presence with a specified intensity may also be derived. If any daily intensity is missing in the considered period, then the number of days of presence is set to missing.

In the solicited period, the Number of days of Presence is categorized as 1-3 days, 4-7 days, 8-14 days, 15-21 days, 22 days or more post-vaccination. If any daily intensity is missing in the considered period, and if the number of days with a presence stays in the same range when adding the number of days with missing daily presence, then the number of days of presence range can be set to this category, and so it will not be missing. Otherwise, the number of days of presence range is set to missing. The same applies to the overall period, with the ranges 1-3 days, 4-7 days, and 8-14 days, 15-21 days, 22 days or more.

5.2.1.1.6 Ongoing

Status Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 5.2.1.1.1:

- 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: other exclusive conditions (ie, it is not included in the denominator of such analysis in safety tables).

5.2.1.2 Unsolicited AEs

5.2.1.2.1 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.

5.2.1.2.2 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 14 and 15 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.

5.2.1.2.3 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 an unsolicited AE has a partially missing start date and there is clear evidence about the last vaccination from the partially missing start date, then the start date is used to determine the last vaccination before the unsolicited. Situations may happen as:
    - If the start date of AE has missing Day and non-missing Month and Year
        - If the "Month/Year of vaccination (i) date" < "Month/Year of AE start date" < "Month/Year of vaccination (i+1) date", then it is clear that the last vaccination before this unsolicited AE is the vaccination i.
        - If the "Month/Year of vaccination (i) date" < "Month/Year of AE start date" and there is no vaccination (i+1), then it is clear that the last vaccination before this unsolicited AE is the vaccination i.

- If the start date of AE has missing Day and Month and non-missing Year:
  - If the "Year of vaccination (i) date" < "Year of AE start date" < "Year of vaccination (i+1) date", then it is clear that the last vaccination before this unsolicited AE is the vaccination i.
  - If the "Year of vaccination (i) date" < "Year of AE start date" and there is no vaccination (i+1), then it is clear that the last vaccination before this unsolicited AE is the vaccination i.

- If the start date is missing or partially missing (with no clear evidence about the last vaccination), 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

5.2.1.2.4 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 5.2.1.2.3.

Time of Onset = start date of the unsolicited AE – date of last vaccination before the unsolicited AE + 1

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

Unsolicited AE that occurred before vaccination (negative time of onset) will not be included in analysis but will be listed separately.

Unsolicited AE which is non-serious, non-AESI and non-MAAE that occurred with a time of onset higher than defined above will not be included in analysis but will be listed separately.

- For unsolicited AE with missing day, month and year, the unsolicited AE will be classified as "Within 28 days"
- For unsolicited AE with partially missing start date, the partial available information will be used to determine if this AE is classified "Within 28 days" or "Not within 28 days". An AE will be categorized as "Not within 28 days" only if there is clear evidence from the partially missing start date that this AE happens before the first vaccination, or after the first vaccination + 28 days but before the second vaccination, or after the second vaccination + 28 days. In all other situations, this AE is considered as "Within 28 days". Situations may happen as:
  - If the start date of AE has missing Day and non-missing Month and Year
    - If the "Month/Year of AE start date" < "Month/Year of first vaccination date", then it is clear that this unsolicited AE happened before the first vaccination.
    - Else if the "Month/Year of last vaccination date" <= "Month/Year of AE start date" <= "Month/Year of (last vaccination date + 28 days)", then this unsolicited AE will be categorized as "Within 28 days".
    - Else if the "Month/Year of AE start date" > "Month/Year of (last vaccination date + 28 days)", then this unsolicited AE will be categorized as "not within 28 days".

- If the start date of AE has missing Day and Month and non-missing Year:
  - If the "Year of AE start date" < "Year of first vaccination date", then it is clear that this unsolicited AE happens before the first vaccination.
  - Else if the "Year of last vaccination date" <= "Year of AE start date" <= "Year of (last vaccination date + 28 days)", then this unsolicited AE will be categorized as "Within 28 days".
  - Else if the "Year of AE start date" > "Year of (last vaccination date + 28 days)", then this unsolicited AE will be categorized as "not within 28 days".

The unsolicited AEs will be analyzed "within 28 days" after each vaccination, which corresponds to AEs with a time of onset between 1 and 29 days. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 5.2.1.2.3), 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.

5.2.1.2.5 Duration

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

- Duration= 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

5.2.1.2.6 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

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

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

5.2.1.2.7 Serious Adverse Events

An event will be considered 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 each and any vaccination
- During the study (i.e., all SAEs occurred during the study)

5.2.1.2.8 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 from D01 to the end of the study

[redacted]

Those AESIs will be analyzed using the following periods:

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

5.2.1.2.9 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

5.2.2 Immunogenicity

5.2.2.1 Computed Values for Analysis

In order to appropriately manage extreme values (< LLOQ and ≥ 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

5.2.2.2 Potential RSV seropositivity

In the statistical analyses, potential RSV seropositivity is determined using two data sources:

1. The stratification factor recorded in the Interactive Response Technology (IRT) system at the randomization
2. Information collected in the eCRF, including maternal RSV immunization and previous receipt of RSV monoclonal antibody

Study participants will be categorized as either potential RSV seropositivity as Yes or No at baseline based upon maternal immunization, previous receipt of RSV monoclonal antibody with the following definitions:

- Potential RSV seropositivity: Yes
  - Participant's biological mother's receipt administration of an RSV vaccine during pregnancy and/or breastfeeding

    OR

- Participant receipt of an RSV monoclonal antibody before study intervention administration

- Potential RSV seropositivity: No
  - Participant's biological mother did not receipt administration of an RSV vaccine during pregnancy and/or breastfeeding

    AND
  - Participant did not receipt any RSV monoclonal antibody before study intervention administration

The potential seropositivity in statistical analyses will be based on the stratification factor recorded in the interactive response technology (IRT) system.

5.2.2.3 Baseline Serostatus

Following study inclusion, the assessment of prior infection status of participants at baseline will be based on exposure to RSV. Baseline serostatus will be determined from serum samples collected at Visit 01 (D01). Study participants will be categorized as either RSV-naïve participants or RSV-exposed participants with the following definitions:

- RSV-naïve participants: participants with no prior exposure to RSV defined as:

  [redacted]

- RSV-exposed participants: participants with prior exposure to RSV infection defined as:

  [redacted]

Baseline Serostatus will be defined as "Undetermined" otherwise.

RSV antibody detection is determined using laboratory-established thresholds (2): anti-F IgA levels ≥ 5.6 AU/mL and anti-G IgG levels ≥ 12.3 AU/mL indicate detection, while values below these thresholds are considered no detection in this algorithm.

Table 5.1: [redacted]

[redacted]

RSV-naïve participants will be categorized as seronegative or passive positive at baseline determined from serum samples collected at Visit 01 (D01) with the following definitions:

- Seronegative: No detection of either anti-F IgA antibodies nor anti-F IgG antibodies nor anti-G IgG antibodies
- Passive positive:

  [redacted]

  [redacted]

Passive immunity status will be defined as "Undetermined" otherwise.

For anti-F IgG, value above or equal to LLOQ (1.6 AU/mL) indicates detection, while values below these thresholds are considered no detection.

5.2.3 Other Safety Endpoints

5.2.3.1 Pregnancy

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

5.2.3.2 Action Taken

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

5.2.3.3 Seriousness

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

5.2.3.4 Outcome

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

5.2.3.5 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 Section 4.4.6.1.2. Relationship to study procedure is only presented in the listing.

5.2.3.6 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 participant who, on the "End of Study Intervention Phase" form question "What was the subject's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "End of Study Intervention Phase" form question "What was the subject's status?" has "Adverse Event" 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.

5.2.4 Derived Other Variables

5.2.4.1 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

5.2.4.2 Duration of a Participant in the Trial

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.

5.2.4.3 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) - minimum for all participants (date of Visit 01) +1.

6. Changes in the Conduct of the Trial or Planned Analyses

Given the decision to halt the trial prematurely, some analyses presented in the study protocol version 3.0 are not applicable anymore.

Indeed, due to the premature stop of the study:

- no participant has received the second vaccination,
- no blood sample has been performed 28 days post-dose 2 (D85)
- no nasal sample has been performed 28 days post-dose 2 (D64)
- [redacted]

Analyses changes are presented in the following subsections.

Primary completion analysis planned to be conducted prior to the final analysis will not be performed.

No participants will fulfill criteria to be included in the PPAS. As a consequence, immunogenicity analyses will be performed only on FAS.

All analyses will only be descriptive.

Considering context of stopping trial/project and limited data, several summary statistical analyses usually provided have been replaced by listings for a simplified report.

Impact on the objectives presented in the study protocol are presented in the following subsections.

6.1 General considerations

Primary completion analysis planned to be conducted prior to the final analysis will not be performed.

No participants will fulfill criteria to be included in the PPAS. As a consequence, immunogenicity analyses will be performed only on FAS.

All analyses will only be descriptive.

Considering context of stopping trial/project and limited data, several summary statistical analyses usually provided have been replaced by listings for a simplified report

Impact on the objectives announced in the study protocol are presented in the following subsections.

6.2 Primary Objectives

6.2.1 Immunogenicity

Due to the halt of the study:

- no participant has received the second vaccination,
- no blood sample has been performed 28 days post-dose 2 (D85)

As no data is available, the non-inferiority analysis cannot be performed.

6.2.2 Safety

Safety analysis will be performed on Safas. Only safety within 28 days after first vaccination and during the study will be applicable. Safety within 28 days after second vaccination will not be applicable as no participant received second vaccination.

- Solicited reactions: summary tables will be presented, details on time period, maximum intensity, time of onset period, range of number of days of presence, action taken will be presented in a listing
- Unsolicited AE: unsolicited AEs within 28 days after vaccination 1 are presented, in summary and by System organ class and preferred term. Details on relationship, intensity, time to onset, duration and whether the AE led to early termination from the study will be presented in a listing.

MAAE, AESI, SAE that occur 28 days after the first vaccination and during the study are presented in the summary table. Details are provided in listings.

6.3 Secondary objectives

6.3.1 Immunogenicity

As no immunogenicity data are available due to no vaccination 2, only RSV serum anti-F IgA, anti-F IgG antibody titers and anti-G IgG antibody titers at D01 are described as scheduled in the protocol.

PRNT testing is not scientifically justified given the clinical hold, early termination, and limited sample size. Available samples are baseline specimens only, collected pre-immunization. Without post-immunization timepoints, immunogenicity assessment (fold-rise, seroconversion, or immune response evaluation) is impossible, and the data are insufficient for meaningful statistical analysis or robust conclusions. Therefore, the PRNT testing was not conducted, and RSVA and RSVB serum neutralizing antibody titers at D01 and D85 are not included in this analysis.

6.3.2 Vaccine virus shedding

As no participants received the second vaccination, no data are available for D64 nasal samples. Only D08 nasal samples results will be described.

6.4 Exploratory objectives



7. Supporting Documentation

7.1 Appendix 1 List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AR	Adverse reaction
CI	Confidence interval
CRF	Case report form
D	Day
DMC	Data Monitoring Committee
FAS	Full analysis set
GM	Geometric mean
GMT	Geometric mean of titer
GMTR	Geometric mean of titer ratio
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IRT	Interactiv response technology
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
NA	Not applicable
NC	Not computed
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse event
SafAS	Safety analysis set
SAP	Statistical analysis plan
SOC	System organ class
PT	Preferred term
TLFs	Tables, listings and figures
ULOQ	Upper level of quantitation

8. References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

2. QU-OPE-2774112 Assessment for Determining RSV F IgA and RSV G IgG Serostatus Thresholds in ECL Methods