Safety, Immunogenicity, Infectivity, and Dose-Finding Study of an Investigational Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccine in Infants and Toddlers

Phase I/II, randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 and 2 administrations of the live-attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine in infants and toddlers 6 to 18 months of age in the United States, Canada, Latin America, and South Africa

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VAD00001
Development Phase:	Phase I/II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	Live Attenuated Respiratory Syncytial Virus (RSV) ΔNS2/Δ1313/I1314L vaccine
Form / Route:	Suspension of virus / Intranasal
Indication For This Study:	Active immunization of infants and toddlers 6 to 18 months of age for the prevention of medically attended lower respiratory tract illness
Version and Date of the SAP core body part:	Version 3.0 30th of March 2023

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List of Abbreviations

Ab	antibody
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
BL	blood sample
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
D	day
DAIDS	Division of AIDS
DC	diary card
eDC	electronic diary card
eCRF	electronic case report form
FAS	full analysis set
Gcc	G (glycoprotein) central conserved region
GMT	geometric mean titer
GMTR	geometric mean titer ratio
Ig	immunoglobulin
LID	Laboratory of Infectious Diseases
LLOQ	lower limit of quantification
LRI	lower respiratory illness
MA	memory aid
MAAE	medically attended adverse event
MAARI	medically attended acute respiratory illness
MAALRI	medically attended acute lower respiratory tract illness
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NR	not reportable
[redacted]	[redacted]
PFU	plaque forming units

PPAS	per-protocol analysis set
PRNT	plaque-reduction neutralization assay
PSB	Product Safety Board
PT	preferred term
RCDC	Reverse cumulative distribution curve
RSV	Respiratory Syncytial Virus
RSV MAARI	RSV-associated, medically attended acute respiratory illness
RSV MAALRI	RSV-associated, medically attended acute lower respiratory tract illness
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class (primary)
ULOQ	upper limit of quantification
V	visit
VE	vaccine efficacy

1 Introduction

This is a study using the investigational RSV ΔNS2/Δ1313/I1314L vaccine (RSVt vaccine) against respiratory syncytial virus (RSV) disease in infants and toddlers.

The RSVt vaccine candidate was originally derived using reverse genetics by the Laboratory of Infectious Diseases (LID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). Based on Phase I trial data, RSVt vaccine appears to be safe and immunogenic and is evaluated by Sanofi Pasteur for further clinical development.

This phase 1/2 study is the first study in Sanofi Pasteur clinical development pathway and will be used to select the most promising dose of vaccine for future studies.

2 Trial Objectives

2.1 Primary Objectives

Primary Safety Objective:

- To assess the safety profile of each dose of RSV ΔNS2/Δ1313/I1314L after each and any administration in all infants and toddlers regardless of baseline serostatus.

Primary Immunogenicity Objective:

- To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 in RSV-naive participants.

2.2 Secondary Objectives

Secondary Safety Objectives:

- To quantify the amount of vaccine virus shed by each participant on D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4, measured by [redacted] by baseline serostatus.

Secondary Infectivity Objective:

- To determine the proportion of vaccinated infants and toddlers in each vaccine group infected[1] with the vaccine virus at D56 (56 days after vaccination 1) for Cohorts 1, 2, 3 and 4, and at D84 (28 days after vaccination 2) for Cohorts 2 and 4 by baseline serostatus.

[1] Infection defined as detection of vaccine virus strain in nasal swab sample by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers and / or RSV serum anti-F IgG antibody titers.

Secondary Immunogenicity Objectives:

- To characterize the RSV A serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) in Cohorts 2 and 4 in RSV-experienced participants.
- To characterize RSV serum anti-F IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize RSV serum antibody responses (RSV A-neutralizing and anti-RSV F IgG) to the study product in each vaccine group after the RSV surveillance season or at least 5 months after the last vaccine administration by baseline serostatus.

2.3 Exploratory Objectives

Exploratory Safety Objective

- To assess the safety profile of each dose of RSV after each and any administration by baseline serostatus.

Exploratory Immunogenicity Objectives:

- To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV A serum neutralizing antibody responses to the study product converted to IU/mL values after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV B serum neutralizing antibody responses to the study product converted to IU/mL values after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize RSV A and RSV B serum anti-protein G central conserved region (anti-Gcc) IgG antibody responses to the study product in each vaccine group after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.

- To characterize RSV A and RSV B serum anti-Gcc IgG antibody responses to the study product in each vaccine group after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.
- To characterize the RSV serum anti-F IgA antibody responses after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 by baseline serostatus.
- To characterize the RSV serum anti-F IgA antibody responses after the RSV season or at least 5 months after the last vaccine administration by baseline serostatus.

Exploratory Efficacy Objective

- To describe the frequency and severity of RSV-associated, medically attended acute respiratory illness (RSV MAARI) and RSV-associated, medically attended, acute lower respiratory illness (RSV MAALRI) in all infants and toddlers in each vaccine group during the RSV season or at least 5 months after last vaccine administration.

3 Description of the Overall Trial Design and Plan

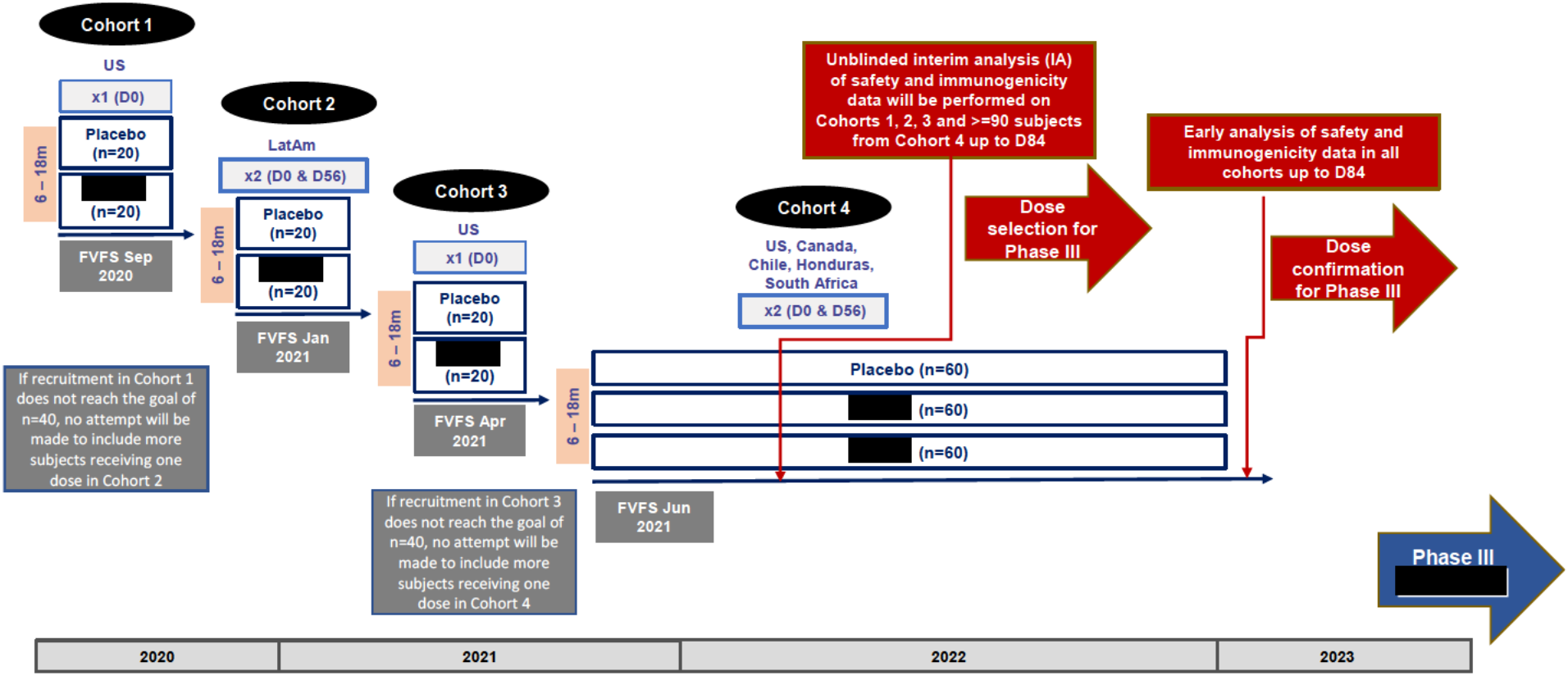
3.1 Trial Design

This is a Phase I/II, randomized, observer-blind, placebo-controlled, multi-center, dose-finding study to evaluate the safety, immunogenicity, infectivity, and vaccine virus shedding after 1 or 2 administrations of a live-attenuated RSVt vaccine in infants and toddlers 6 months to 18 months of age in the United States, Canada, Latin America (Argentina, Chile, and Honduras), and South Africa.

A total of 300 infants and toddlers 6 to 18 months of age will be enrolled into 1 of 4 cohorts, sequentially, and within each cohort will be randomized to receive intranasal administration of their assigned study product as follows:

- Cohort 1 (Northern Hemisphere) – 40 infants and toddlers to receive 1 administration at D0, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo
- Cohort 2 (Southern Hemisphere)– 40 infants and toddlers to receive 2 administrations at D0 and D56, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose) or placebo
- Cohort 3 (Northern Hemisphere) – 40 infants and toddlers to receive 1 administration at D0, 1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo
- Cohort 4 (Northern and Southern Hemisphere) – 180 infants and toddlers to receive 2 administrations at D0 and D56, 1:1:1 ratio of RSV ΔNS2/Δ1313/I1314L [redacted] (low-dose), RSV ΔNS2/Δ1313/I1314L [redacted] (high-dose) or placebo

Figure 3.1: Study design



The scope of the early analysis will be all data for participants from cohort 1,2 and 3, and data up to Day 84 for all participants from the cohort 4.

3.2 Trial Plan

Figure 3.2 and Figure 3.3 provide overviews of the study plan and the timeframes for Cohorts 1 and 3, and Cohorts 2 and 4, respectively. See Tables of Study Procedures (Table 3.1, Table 3.2, Table 3.3) for the plan of activities for the study period.

Figure 3.2: Study Plan and Timeframe for Cohorts 1 and 3

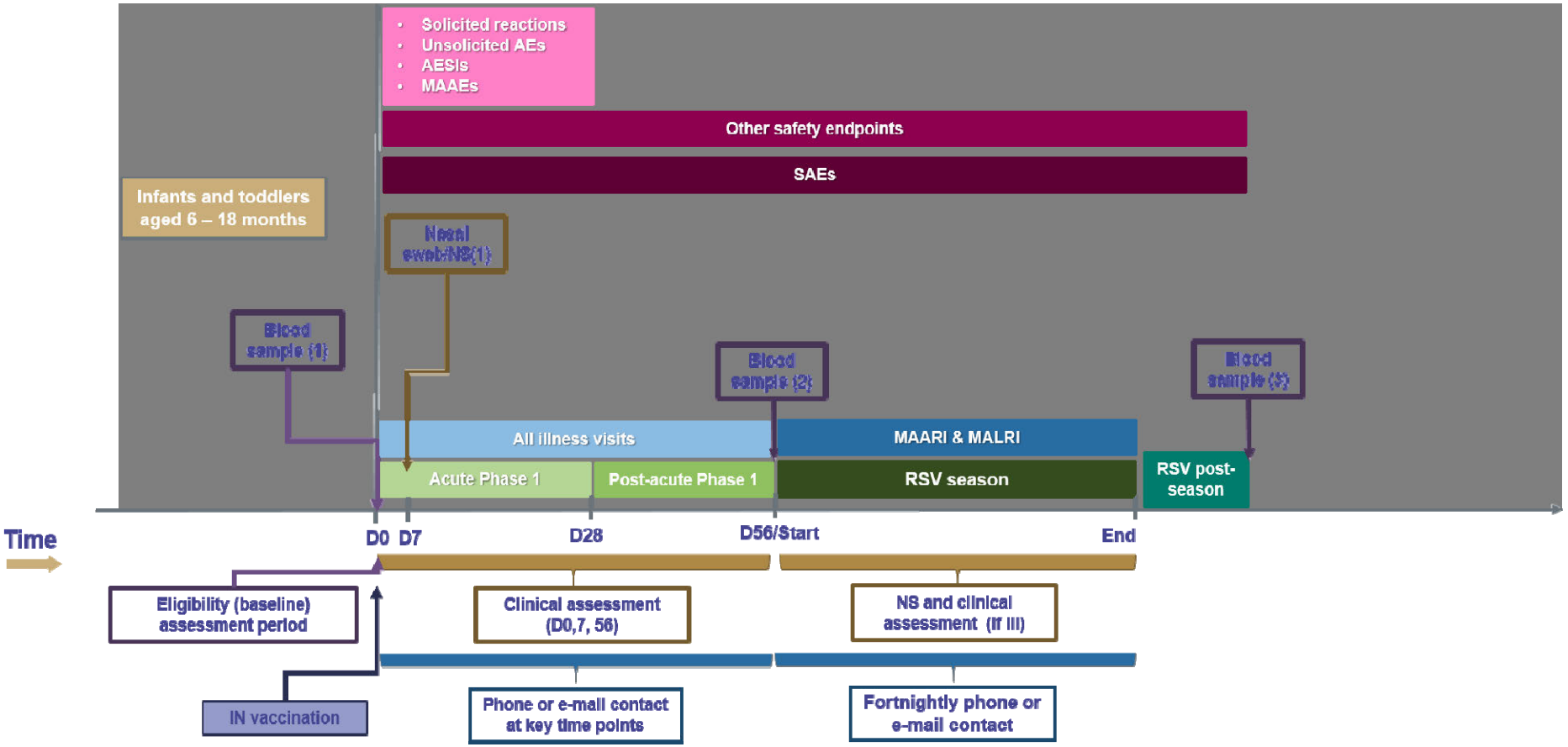


Figure 3.3: Study Plan and Timeframe for Cohorts 2 and 4

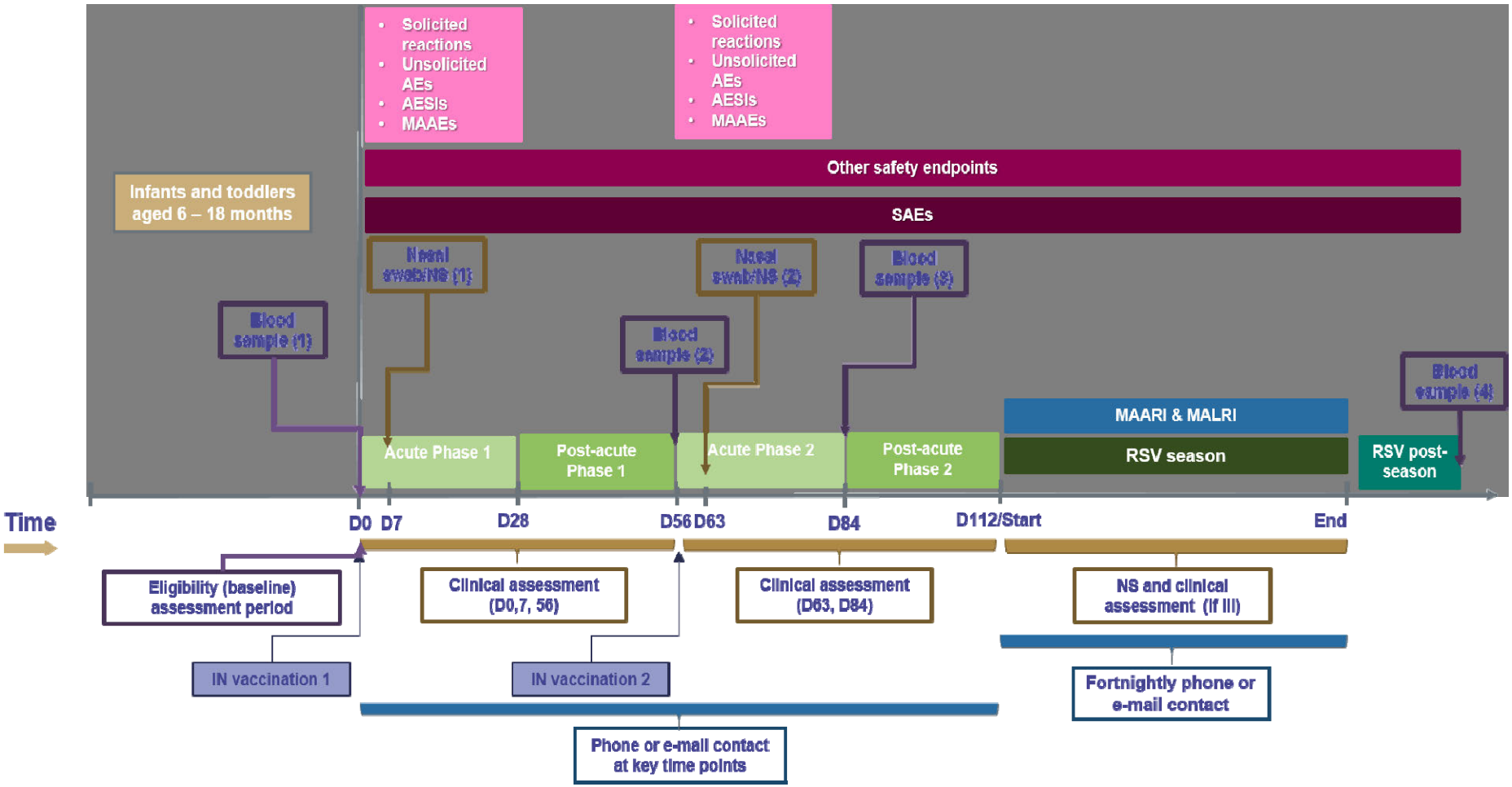


Table 3.1: Table of Study Procedures for Cohorts 1 and 3

Phase I/II Study, 4 Planned Visits, 30 (32) non-visit telephone contacts, 1 Vaccination, 3 Planned Blood Samples, 1 Planned Nasal Swab, up to a Maximum of 12 Months of Participation per Participant

Visit (V) / Contact	**Visit 01**	**Phone contacts 1 - 6**	**Visit 02**	**Phone contacts 7 - 16**	**Phone Contact 17**	**Phone contact 18**	**Visit 03**	**Phone contacts 19 -30 (32)‡‡**	**Visit 04§§**	**Illness Visit(s) Visit 99*** **
Study timelines - Days(D)	**D0**	**Daily (x6)**	**D7**	**Three times weekly (x10)**	**D29 (+1)**	**D42** (+1)	**D56 (+7)**	**Every 2 weeks**	**1 – 30 Apr (NH)**	
In-person visit	X		X				X		X	X
Non-visit contact*		X		X	X	X		X		
Informed consent	X									
Demography data	X									
Inclusion / Exclusion criteria	X									
Medical history and physical examination	X									
Vital signs†	X		X				X			X
COVID-19 test	X									X
Interim history			X				X			X
Focused clinical examination			X				X			X
Collection of reportable concomitant medications/vaccinations							X			X
Allocation participant number	X									
Randomization / Dose number	X									
Blood samples	BL0001						BL0002		BL00P2	
Nasal swab‡			NS0001							NS0001 or UN0001 to UN000X
Vaccination	X									
Immediate surveillance (30 min) §	X									

Visit (V) / Contact	**Visit 01**	**Phone contacts 1 - 6**	**Visit 02**	**Phone contacts 7 - 16**	**Phone Contact 17**	**Phone contact 18**	**Visit 03**	**Phone contacts 19 -30 (32)‡‡**	**Visit 04§§**	**Illness Visit(s) Visit 99*** **
Study timelines - Days(D)	**D0**	**Daily (x6)**	**D7**	**Three times weekly (x10)**	**D29 (+1)**	**D42** (+1)	**D56 (+7)**	**Every 2 weeks**	**1 – 30 Apr (NH)**	
Diary Card (DC) electronic DC (eDC) provided	DC1/eDC		DC2							
DC / eDC reviewed		DC1/eDC **	DC1/eDC	DC1 /eDC **	DC2/eDC **	DC2/eDC**	DC2		X	X
DC collected							DC1/DC2			
Memory aid (MA) provided							X			
MA reviewed									X	X
Collection of solicited local respiratory and systemic reactions††	X	X	X	X	X					
Collection of unsolicited adverse events††	X	X	X	X	X					
Collection of adverse events of special interest††	X	X	X	X	X					
Collection of medical attended adverse events††	X	X	X	X	X					
Collection of serious adverse events	X									

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.
† Vital signs will be collected in the eCRF.
‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D7, i.e., 7 days after vaccination. The same nasal swab specimens may also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D7 visit.
§Any unsolicited systemic adverse events occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic adverse events in the case report book.
**Diary Card (DC) / Electronic Diary Card (eDC) will be reviewed by telephone contact.
††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 after vaccine administration.
‡‡Phone contact during the RSV season every 2 weeks.

§§Visit 04: Post-RSV season visit in the month after the cessation of the RSV season.
***Illness Visits: Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (see Table 5.4 of the protocol) including medically attended visits during RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. 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. The requirement for an onsite or at home illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

Table 3.2: Table of Study Procedures for Cohorts 2 and 4 – Vaccination 1 (D0 to D55)

Phase I/II Study, 6 Planned Visits, 40 (42) Non-visit Telephone Contacts, 2 Vaccinations, 4 Planned Blood Samples, 2 Planned Nasal Swabs, up to a Maximum of 12 Months of Participation per Participant

Visit (V) / Contact	**Visit 01**	**Phone contacts 1-6**	**Visit 02**	**Phone contacts 7-16**	**Phone contact 17**	**Phone contact 18**	**Illness Visit(s) ‡ Visit 99**
Study timelines – Days (D)	**D0**	**Daily (x6)**	**D7**	**Three times weekly (x10) between D8 and D28**	**D29** (+1)	**D42** (+1)	**Any time between Visit 01 and Visit 06**
In-person visit	X		X				X
Non-visit contact*		X		X	X	X	
Informed consent	X						
Demography data	X						
Inclusion / Exclusion criteria	X						
Medical history and physical examination	X						
Vital signs†	X		X				X
COVID-19 test	X						X
Interim history			X				X
Focused clinical examination			X				X
Collection of reportable concomitant medications/ vaccinations							X
Allocation of participant number	X						

Visit (V) / Contact	**Visit 01**	**Phone contacts 1-6**	**Visit 02**	**Phone contacts 7-16**	**Phone contact 17**	**Phone contact 18**	**Illness Visit(s) ‡ Visit 99**
Study timelines – Days (D)	**D0**	**Daily (x6)**	**D7**	**Three times weekly (x10) between D8 and D28**	**D29** (+1)	**D42** (+1)	**Any time between Visit 01 and Visit 06**
Randomization / Dose number	X						
Blood samples	BL0001						
Nasal swabs‡			NS0001				NS0001 or UN0001 to UN0000X
Vaccination (1st administration)	X						
Immediate surveillance (30 min) §	X						
Diary Card (DC) / electronic DC (eDC) provided	DC1/eDC		DC2				
DC / eDC reviewed		DC1/eDC**	DC1/eDC	DC1/eDC **	DC2/eDC **	DC2/eDC **	X
Collection of solicited local respiratory and systemic reactions**	X	X	X	X	X		
Collection of unsolicited adverse events**	X	X	X	X	X		
Collection of adverse events of special interest**	X	X	X	X	X		
Collection of medical attended adverse events**	X	X	X	X	X		
Collection of serious adverse events	X						

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.
† Vital signs will be collected in the eCRF.
‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D7, i.e., 7 days after vaccination 1. The same nasal swab specimen may also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D7 visit.
§Any unsolicited systemic adverse events occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic adverse events in the case report book.
**Diary Card / Electronic Diary Card (DC / eDC) will be reviewed by telephone contact.
††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D0 to D28 after vaccine administration 1 (Acute phase 1).
‡‡Illness Visits (between V01 and V06): Additional nasal swab specimens for the detection of RSV and respiratory pathogens" (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (see Table 5.4 of the protocol) including medically attended visits during RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. 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. The requirement

for an at home or onsite illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

Table 3.3: Table of Study Procedures for Cohorts 2 and 4 – Vaccination 2 (D56 to End of Study)

Phase I/II Study, 6 Planned Visits, 40 (42) Non-visit Telephone Contacts, 2 Vaccinations, 4 Planned Blood Samples, 2 Planned Nasal Swabs, up to a Maximum of 12 Months of Participation per Participant

Visit (V) / Contact	**Visit 03**	**Phone contacts 19-24**	**Visit 04**	**Phone contacts 25-30**	**Visit 05**[†††]	**Phone contact 31 – 40 (42)**[‡‡]	**Visit 06**[‡‡]	**Illness Visit(s)** [***] **Visit 99**
Study timelines – Days (D)	**D56+7**	**Daily (x6)**	**D63 (+7)**	**Twice weekly (x6) between D64 and D83**	**D84 (+8)**	**Every 2 weeks between Visit 05 and Visit 06**	**1 – 31 Oct (SH) 1 – 30 Apr (NH) or > 5 months after last vaccine admin.**	**Any time between Visit 01 and Visit 06**
In-person visit	X		X		X		X	X
Non-visit contact[*]		X		X		X		
Vital signs[†]	X		X		X			X
Interim history	X		X		X			X
Focused clinical examination	X		X		X			X
COVID-19 test	X							X
Collection of reportable concomitant medications/ vaccinations	X							X
Dose Number	X							
Blood samples	BL0002				BL0003		BL00P2	
Nasal swabs [‡]			NS0002					NS0002 or UN0001 to UN000X
Vaccination (2nd administration)	X							
Immediate surveillance (30 min) [§]	X							
Diary Card (DC1)	DC3							
DC / eDC reviewed[**]	DC2/eDC	DC3/eDC [**]	DC3/eDC	DC3/eDC [**]	DC3/eDC		X	X

Visit (V) / Contact	**Visit 03**	**Phone contacts 19-24**	**Visit 04**	**Phone contacts 25-30**	**Visit 05†††**	**Phone contact 31 – 40 (42)‡‡**	**Visit 06‡‡**	**Illness Visit(s) *** Visit 99**
Study timelines – Days (D)	**D56+7**	**Daily (x6)**	**D63 (+7)**	**Twice weekly (x6) between D64 and D83**	**D84 (+8)**	**Every 2 weeks between Visit 05 and Visit 06**	**1 – 31 Oct (SH) 1 – 30 Apr (NH) or > 5 months after last vaccine admin.**	**Any time between Visit 01 and Visit 06**
DC collected	DC1/DC2				DC3			
Memory aid (MA) provided					X			
MA reviewed							X	X
Collection of solicited local respiratory and systemic reactions††	X	X	X	X	X			
Collection of unsolicited adverse events††	X	X	X	X	X			
Collection of adverse events of special interest††	X	X	X	X	X			
Collection of medical attended adverse events††	X	X	X	X	X			
Collection of serious adverse events	X							

*Non-site visit contacts are to be made by phone at scheduled timepoints in the study.
† Vital signs will be collected in the eCRF.
‡All participants will provide a nasal swab sample for quantification of vaccine virus shedding at D63, i.e., 7 days after vaccination 2. The same nasal swab specimen will also be tested for respiratory pathogens (including COVID-19), if the participant is ill at the time of D63 visit.
§Any unsolicited systemic adverse events occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic adverse events in the case report book.
**Diary Card (DC) / Electronic Diary Card (eDC) will be reviewed by telephone contact.
††The participant's parent / guardian / legally authorized representative will record information in a DC / eDC about solicited reactions, unsolicited AEs, AESIs and MAAEs from D56 to D84(Acute phase 2)
‡‡Phone contact during the RSV season, every 2 weeks.
§§Visit 06: Post-RSV season visit – In the month after the cessation of the RSV season in sites with differing seasons or at least 5 months after last vaccine administration. Study participants enrolled during the routine RSV season (ie November to March for NH and May to September for SH) will be followed up for at least 5 months after the last vaccine administration.
***Illness Visits (between V01 and V06): Additional nasal swab specimen for the detection of RSV and respiratory pathogens (including COVID-19) will also be collected from participants during illness visits and 48 hours later at any other protocol specified time point in the study (see Table 5.4 of the protocol) including medically attended visits during the RSV season. If a participant visits any other non-study doctor / hospital for a serious adverse event (SAE) at any time in the study, a nasal swab sample will be obtained at the study site once the participant is discharged, if deemed appropriate by the study investigator. 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. The requirement for an at home or onsite illness visit will be evaluated first by video call to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

††† Visit 05 is to occur 84 days after the first vaccination at Visit 01 and 28 days after the second vaccination visit at Visit 03.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Safety

See Section 9.1.1 of the protocol.

4.1.2 Infectivity

There are no primary objectives for infectivity.

4.1.3 Immunogenicity

See Section 9.1.3 of the protocol.

4.1.4 Efficacy

There are no primary objectives for efficacy.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Safety

See Section 9.2.1 of the protocol.

4.2.2 Infectivity

See Section 9.2.2 of the protocol.

4.2.3 Immunogenicity

See Section 9.2.3 of the protocol.

4.2.4 Efficacy

There are no secondary objectives for efficacy.

4.3 Exploratory Endpoints and Assessment Methods

4.3.1 Safety

See Section 9.3.1 of the protocol.

4.3.2 Infectivity

There are no exploratory objectives for infectivity.

4.3.3 Immunogenicity

See Section 9.3.3 of the protocol.

4.3.4 Efficacy

See Section 9.3.4 of the protocol.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 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, Grade 4, Grade 5 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 9.1.1.3.2 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.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

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

- None: No presence

- Grade 1, Grade 2, Grade 3, Grade 4, Grade 5: 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 D0-D3, D4-D7, D8-D14, D15-D28, D29 or later.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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 D0-D3, D4-D7, D8-D14, D15-D28.

4.4.1.1.5 Number of Days of Presence During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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, 15-28 days, 29 days.

4.4.1.1.6 Overall Number of Days of 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, 15-28 days, 29 days or more, and Missing end date.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 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).

4.4.1.2 Unsolicited AEs

4.4.1.2.1 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.

4.4.1.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing. For AESI (except wheezing), intensity will be graded using the following classification: None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 or Missing as defined in Section 9.1.1.3.5 of the protocol.

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 Section 9.1.1.3.2 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.

4.4.1.2.3 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 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.

4.4.1.2.4 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 4.4.1.2.3:

- 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 0 and 28 days. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.4.1.2.3), so will be included in these tables.

Time of onset period is displayed as D0-D3, D4-D7, D8-D14, D15 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.

4.4.1.2.5 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.

4.4.1.2.6 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:

- Acute otitis media
- Upper respiratory tract illness (URI)
    - Pharyngitis
    - Cough without LRI
- Lower respiratory tract illness (LRI)
    - Stridor
    - Rales
    - Tachypnea
    - Acute wheeze
    - Pneumonia
    - Laryngotracheobronchitis

4.4.1.2.7 Medically Attended Adverse Events

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

4.4.1.2.8 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 vaccination
- During the study (i.e., all SAEs occurred during the study)

4.4.1.2.9 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 "Completion at End of Study" form question "What was the participant'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 participant'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.

4.4.1.3 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

4.4.2 Immunogenicity

4.4.2.1 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 ([redacted]) for the calculation instead of the LLOQ.

Note for titers converted into IU/mL:

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

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

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.

4.4.2.2 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 ([redacted]) for the calculation instead of the 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.

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

4.4.2.3 Baseline serostatus

For this Sanofi Phase I/II trial, baseline serostatus will be determined from serum samples collected at baseline (V01). Participants will be categorized into RSV-experienced or RSV-naïve based on the presence or absence of detectable RSV 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 [redacted]
- ***RSV-experienced*** for participants with baseline IgA titer [redacted]
- ***Undetermined*** for participants with baseline IgA titer 'missing' or 'NR'.

4.4.3 Efficacy

The following events will be collected in the database during illness visits:

- Fever
- Acute otitis media
- Upper respiratory tract illness:
  - Rhinorrhea
  - Nasal congestion
  - Pharyngitis
  - Cough without LRI
- Lower respiratory tract illness
  - Stridor
  - Rales
  - Tachypnea
  - Acute wheeze
  - Pneumonia
  - Laryngotracheobronchitis

A diagnosis of RSV MAARI requires the documentation of any of the events described above, associated with a respiratory sample positive for RSV by [redacted].

A diagnosis of RSV MAALRI (a subset of MAARI) requires the documentation of any of the lower respiratory tract illness events described above, associated with a respiratory sample positive for RSV by [redacted].

4.4.4 Derived Other Variables

4.4.4.1 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

4.4.4.2 Participant duration

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

4.4.4.3 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.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software 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 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of participants. 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. Unsolicited: Number and percentage (95% CIs) of participants, and number of events.
Immunogenicity / Shedding results	**Categorical data (cutoff)**	Number and percentage (95% CIs) 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. Graphical representation by Reverse Cumulative Distribution Curve (RCDC) for immunogenicity.
Infectivity results	**Categorical data**	Number and percentage (95% CIs) of participants.
Efficacy results	**Categorical data**	Number and percentage (95% CIs) of participants, number of events, Vaccine Efficacy (VE) and 95% CI.

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

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/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,…,y_n) are the observed titers or individual ratios for each participant.

CIs for VE will be calculated using the Exact method described by Breslow & Day (2).

5.1 Statistical Methods

Statistical analyses will be conducted by cohort and cohorts pooled, as applicable on specific periods of time (e.g., D0-D56 after vaccination 1 for Cohorts 1, 2, 3 and 4; D56-D84 after vaccination 2 for Cohorts 2 and 4).

When applicable, analyses will be presented by baseline serostatus and overall.

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

5.1.1.1 Hypotheses

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

5.1.1.2 Statistical Methods

The data for any participant infected by laboratory confirmed wt RSV will be excluded from immunogenicity and viral shedding analyses from the date of wt RSV infection.

A short complementary analysis will be done without the exclusion of data to compare results.

Safety

Solicited adverse reactions (ARs), unsolicited AEs (including SAEs), MAAEs and AESIs will be summarized as described in Table 5.1. The main parameters will be described with 95% CI. At least the following parameters will be presented by vaccine group after each and any vaccination, in all participants regardless of baseline serostatus:

- Unsolicited systemic AEs occurring within 30 minutes of administration (immediate unsolicited AEs)

- Solicited administration site reactions and solicited systemic reactions within 28 days after each and any administration according to presence, time period, time of onset, intensity, number of days of presence, action taken, and whether the reaction led to early termination from the study. When more than 1 intensity level is reported within a time period, the highest intensity will be used.
- Unsolicited AEs occurring within 28 days after each and any administration by system organ class (SOC) and preferred term (PT), relationship, intensity, time of onset, duration and whether the AE led to early termination from the study.
- All SAEs that occur throughout the study by SOC and PT, seriousness criteria, time of onset, outcome, relationship, and whether the SAE led to early termination throughout the study
- All MAAEs and AESIs reported within 28 days after each and any vaccination by SOC and PT and relationship

Bayesian approach

A Bayesian approach based on Posterior Distribution may be applied to assess the difference between each RSV formulation and placebo group on the following safety endpoints (and/or other endpoint of interest):

- Any Grade ≥ 3 LRI
- Grade 3 fever

The probability that the difference of percentages of events between one RSV formulation and Placebo is greater than a pre-specified margin (δ) can be calculated based on posterior distribution, using non-informative prior Beta (1,1) (3) and observed binomial data:

Proba (%RSV - %Placebo > δ)

With:
- %RSV = (number of events / number of participants) in RSV group
- %Placebo = (number of events / number of participants) in Placebo group

If this probability is high (e.g., >=80%) then it may be recommended to drop the formulation.

To assess the Bayesian probability that the percentage of events in RSV group is greater than a predefined value (δ) in comparison to Placebo, the posterior distribution of the difference (RSV - Placebo) would be computed using:

- a non-informative prior distribution: incidence of events in each group (p_i) follows uniform distribution (0,1)
- the likelihood of the observed data: Binomial distribution (n_i, p_i), n_i= number of assessed participants in each group, p_i= incidence of the events in each group
- The posterior distribution is the density distribution of the parameter P_i combining 1) the prior distribution and 2) the observed data.

- Posterior distribution: Beta (x_i+1, n_i-x_i+1), where x_i= number of events in each group and n_i = number of assessed participants in each group

- From the density distribution of P_{RSV} and $P_{Placebo}$, determine the density of the groups difference: simulate 1 000 000 pairs of observations and determine the proportion of difference (P_{RSV}- $P_{Placebo}$) > δ.

Immunogenicity

The point estimates and their 95% CI of the following parameters will be presented for RSV A neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, for each vaccine group in RSV-naive participants:

- GMT
- GMTR based on the baseline neutralizing Ab titer
- Seroresponse rates defined as percentage of participants with a ≥ 4-fold rise in RSV A serum neutralizing antibody titers based on the baseline value.
- Reverse cumulative distribution curves (RCDCs) will be presented
- Pairwise comparisons between vaccine groups may be conducted as exploratory analyses to compare seroresponse rates or GMTs for descriptive purpose.

The 95% CIs of the difference of proportions between 2 groups would be computed using the Wilson Score method without continuity correction. CIs of ratio of GMTs between 2 groups will be computed from the difference in means of log10 transformed titers between 2 groups with normal approximation.

Seroresponse using various thresholds regarding fold-rise or post-vaccination titer value may also be presented, as applicable. 4-fold rise seroresponse rate may be also presented by country/racial origin.

A Bayesian approach may be also applied to assess the seroresponse rate of RSV formulation by calculating the Bayesian probability that the percentage of participants with a ≥ 4-fold rise in RSV A serum neutralizing antibody titers is greater than a predefined value.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

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

5.1.2.2 Statistical Methods

Safety

The point estimates and their 95% CI of the following parameter will be presented 7 days after each vaccination (D7 for Cohorts 1, 2, 3 and 4, and D63 for Cohorts 2 and 4) for each vaccine group by baseline serostatus:

- Proportion of participants with detectable/quantified virus shedding
- Arithmetic mean of vaccine virus shedding measured by [redacted]

Infectivity

The point estimate and its 95% CI of the following parameters will be presented after vaccination 1 (D56) for Cohorts 1, 2, 3 and 4, and after vaccination 2 (D84) for Cohorts 2 and 4 for each vaccine group by baseline serostatus:

- Proportion of vaccinees infected with the vaccine virus. Infection defined as detection of vaccine virus strain in nasal swab by [redacted] and / or a ≥ 4-fold rise in RSV A serum neutralizing antibody titers or RSV serum anti-F IgG antibody titers.

Immunogenicity

The point estimates of GMT and GMTR and their 95% CI will be presented by vaccine group for the following endpoints:

- RSV A serum neutralizing antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4, in RSV-experienced participants
- RSV serum anti-F IgG antibody titers by D56 for Cohorts 1, 2, 3 and 4, and by D84 for Cohorts 2 and 4 by baseline serostatus.
- RSV A serum neutralizing and anti-RSV F IgG antibody titers after RSV season or at least 5 months after last vaccine administration by baseline serostatus.

Seroresponse using various thresholds regarding fold-rise or post-vaccination titer value may also be presented, as applicable.

Main immunogenicity analyses will be presented by baseline serostatus and age group (< 12 months *versus* ≥ 12 months).

5.1.3 Statistical Methods for Exploratory Objectives

Safety

Solicited ARs, unsolicited AEs (including SAEs), MAAEs and AESIs will be summarized. Analyses described in Section 5.1.1.2 will be presented by vaccine group after each and any vaccination by baseline serostatus.

Immunogenicity

Similar analyses as described as for secondary immunogenicity objectives will be performed on exploratory immunogenicity endpoints.

Analyses on RSV A and RSV B serum anti-Gcc IgG antibody responses planned in the protocol will finally not be produced for this study, please refer to section 5.7 for the rationale.

Efficacy

RSV Medically attended respiratory illness collected during the RSV season will be summarized. The main parameters will be described with 95% CI. At least the following parameters will be presented by vaccine group:

- RSV medically attended acute respiratory illness (RSV MAARI) by SOC and PT, intensity, time of onset, and duration
- RSV medically attended lower respiratory tract illness (RSV MAALRI) by SOC and PT, intensity, time of onset, and duration
- Vaccine Efficacy (VE)

The VE of RSVt vaccine (low dose or high dose, as applicable) will be estimated for each endpoint as follows:

$$VE = 1 - \frac{C_{RSV}/N_{RSV}}{C_P/N_P}$$

where:

- C_{RSV} and C_P are the numbers of RSV MAARI / RSV MAALRI cases meeting the considered definition in the RSV (low dose or high dose) and Placebo groups, respectively.
- N_{RSV} and N_P are the numbers of participants in the RSV (low dose or high dose) and Placebo groups, respectively.

The CI will be calculated using the exact method conditional on the total number of cases in both groups described by Breslow & Day (2).

Let $q = \frac{C_{RSV}}{C_{RSV}+C_P}$, the proportion of cases belonging to RSV group (low dose or high dose) among the total number of cases in the considered RSV vaccine group and Placebo group. Given the total number of cases, C_{RSV} has a binomial distribution ($C_{RSV}+C_P$, q). Thus, a CI for q may be constructed using the exact Clopper-Pearson method for binomial proportions (1).

As $\frac{q}{1-q} = \frac{C_{RSV}}{C_P}$, the VE estimate given above may be restated as follows:

$VE = 1 - \frac{C_{RSV}/N_{RSV}}{C_P/N_P} = 1 - \frac{N_P}{N_{RSV}} \times \frac{q}{1-q}$, which is a strictly decreasing function of q.

Finally, for each efficacy endpoint, a CI of the VE will be constructed based on the CI of q.

5.2 Analysis Sets

The following analysis sets will be used: The Full Analysis Set, the Per-Protocol Analysis Set, and the Safety Analysis Set.

5.2.1 Full Analysis Set

The full analysis set (FAS) is defined as the subset of randomized participants who received at least 1 administration of the study vaccine.

5.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those participants who have received at least 1 administration of the study vaccine.

All participants will have their safety analyzed after each administration according to the vaccine they actually received and after any vaccination according to the vaccine received at the first administration.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.3 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. Two specific PPAS will be defined: PPAS1 after 1 administration (for participants in Cohorts 1, 2, 3 and 4) and PPAS2 after 2 administrations (for participants in Cohorts 2 and 4).

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Baseline serology blood sample was not collected at visit 01 (D0).
- Participant with temporary contraindication did not receive vaccination 1 in the proper time window from randomization *[i.e., within 5 days of randomization]*
- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive vaccine / did not complete the vaccination schedule
- Participant received a vaccine other than the one that he / she was randomized
- Preparation and / or administration of vaccine not done as per-protocol
- Participant received a protocol-prohibited therapy before the post-vaccination serology blood sample (see Section 6.7.1 of the protocol)
- Participant with confirmed diagnosis of wild-type (wt) RSV before the post-vaccination serology blood sample
- Participant with an emergency unblinding performed by the Investigator

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS1 only:

- Post-vaccination 1 serology blood sample not collected at visit 03
- Post-vaccination 1 serology blood sample not collected at visit 03 in the proper time window *[i.e., date of vaccination 1 + 56 days; date of vaccination 1 + 66 days]**

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2 only (for participants in Cohorts 2 and 4):

- Participant did not receive vaccination 2 at visit 03 in the proper time window *[i.e., date of vaccination 1 + 56 days; date of vaccination 1 + 66 days]**
- Post-vaccination 2 serology blood sample not collected at visit 05
- Post-vaccination 2 serology blood sample not collected at visit 05 in the proper time window *[i.e., date of vaccination 2 + 28 days; date of vaccination 2 + 38 days]**

In addition to the reasons listed above, participants will also be excluded from the PPAS if their baseline serology sample or their post-vaccination serology sample did not produce a valid test result (i.e., result for RSV A serum neutralizing antibody titers is missing).

Note: For PPAS1 (after 1 administration), timepoints to be considered are: D0 for vaccination and D56 (visit 03) for the post-vaccination serology sample. For PPAS2 (after 2 administrations), timepoints to be considered are: both D0 (visit 01) and D56 (visit 03) for vaccinations and D84 (visit 05) for the post-vaccination serology sample.

The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site. During the review, such deviations will be marked with exclusion from analysis set for programming purpose.

*Time windows have been extended in the PPAS definition compared to study protocol for clinical relevance.

5.2.4 Other Analysis Set

Randomized participants

A randomized participant is a participant for whom a vaccine group has been allocated.

5.2.5 Populations Used in Analyses

The safety analysis will be performed on the SafAS. Participants will be analyzed after each vaccination according to the vaccine they actually received, and after any vaccination according to the vaccine received at the first administration.

Immunogenicity analyses will be performed on the Full Analysis Set and on the Per-Protocol Analysis Set for main immunogenicity parameters. In the FAS, participants will be analyzed by the vaccine group to which they were randomized. In the PPAS, participants will be analyzed according to the vaccine they actually received.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 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.

5.3.1.2 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.

5.3.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.1.4 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 4.4.1.2.3). 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.

5.3.1.5 Action Taken

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

5.3.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.4.2.1.

5.3.3 Efficacy

Missing data will not be imputed. No test or search for outliers will be performed.

5.4 Interim / Preliminary Analysis

The analysis will be performed with a stepwise approach.

- Several blinded early safety data reviews will be performed on safety data collected in participants from each cohort at specific timepoints (see Section 5.1.6 of the protocol).
- An unblinded interim analysis for dose selection of RSVt vaccine is planned on participants from Cohorts 1, 2 and 3, and at least 90 participants enrolled in Cohort 4. The interim analysis will take place when participants have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. This unblinded interim analysis requires the unblinding of data; a specific process will be implemented to maintain the blind at the participant and Investigator levels.
- An unblinded early analysis is planned on participants from all Cohorts (Cohorts 1, 2, 3, and 4). As per protocol the early analysis is planned on all participants when they have provided safety data up to the D84 timepoint and have D84 immunogenicity results available. However, shedding data will be available later than other data, so the analysis will be done in two steps.

  The first step of the early analysis will consider all data except shedding data. Shedding and infectivity outputs will not be part of the first key tables produced.

  Complementary key tables on shedding and infectivity will be produced at the second step.

This early analysis requires the unblinding of all participants. A specific process will be implemented to maintain the blind at the participants and Investigator levels. Based on the results of this analysis, a dose will be confirmed for future studies

- The final unblinded statistical analysis will address the objectives on all participants (Cohorts 1, 2, 3 and 4).

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

5.5 Determination of Sample Size and Power Calculation

No sample size calculation was done as there are no statistical hypotheses in this study.

A total of 300 participants are planned to be enrolled into 1 of the 4 cohorts sequentially:

- Cohort 1 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)
- Cohort 2 (2 administrations): 40 participants, i.e., 20 per vaccine group (RSV low-dose or placebo)
- Cohort 3 (1 administration): 40 participants, i.e., 20 per vaccine group (RSV high-dose or placebo)

- Cohort 4 (2 administrations): 180 participants, i.e., 60 per vaccine group (RSV high-dose or RSV low-dose or placebo).

Although there are no statistically powered hypotheses and no sample size computation in this study, the sample size of 100 participants in the RSV low-dose group (20 from Cohort 1, 20 from Cohort 2 and 60 from Cohort 4) will provide a probability of 95% to observe an event that has a true incidence of 3%. The sample size of 80 participants in the RSV high-dose group (20 from Cohort 3 and 60 from Cohort 4) will provide a probability of 95% to observe an event that has a true incidence of 3.75%.

A total of 300 participants are planned to be enrolled in the study. This corresponds to 120 participants in Placebo group, 100 participants in RSV low-dose group and 80 participants in RSV high-dose group. Table 5.2 below presents the number of participants by serostatus, in total and by RSV group, according to varying possible RSV-experienced rates ranging from 5% to 35% (derived from LID/NIH screening data) and provides a global overview of the proportion of RSV-naive/RSV-experienced participants that will be enrolled in the study.

Table 5.2: Number of Participants by Serostatus, in Total and by RSV Group, According to Varying Possible RSV-experienced Rates Ranging from 5% to 35%

% RSV-experienced	Total (N=300)		RSV low-dose group (N=100)		RSV high-dose group (N=80)	
	#RSV-experienced	#RSV-naive	#RSV-experienced	#RSV-naive	#RSV-experienced	#RSV-naive
5%	15	285	5	95	4	76
10%	30	270	10	90	8	72
15%	45	255	15	85	12	68
20%	60	240	20	80	16	64
25%	75	225	25	75	20	60
30%	90	210	30	70	24	56
35%	105	195	35	65	28	52

5.6 Data Review for Statistical Purposes

No review of data was performed.

5.7 Changes in the Conduct of the Trial or Planned Analyses

Analyses on RSV A and RSV B serum anti-Gcc IgG antibody responses planned in the protocol will finally not be produced for this study. Based on the rationale that serum might not be an efficient matrix to capture Gcc responses, we decided to drop off this readout from the current exploratory analyses plan

6 References List

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