SAP Core Body for Stage 1

Title: A Phase I/IIa, randomized, placebo-controlled multi-arm dose-finding study to evaluate the safety and immunogenicity of a RSV mRNA vaccine candidate in adult participants 18 to 50 years of age in Phase I, and 60 years and older in Phase IIa

Study Code: VAE00010

Study Phase: Phase I/IIa

SAP Core Body Version: 6.0

SAP Core Body Date: 21Jul2025

Protocol Version Number: 7.0

The SAP Code Body should be used in conjunction of the study protocol (Stage 1) and the SAP TLF for Stage 1. This SAP Core Body concerns only Stage 1 of the study, Stage 2 will be handled in another SAP Core Body.

Version History

Previous Version(s)	Date	Comments
1.0	04-Jul-2022	Initial version
2.0	28-Sep-2022	Updates following protocol v5.0 Details added for Bayesian probabilities computation
3.0	28-Feb-2023	Immunogenicity analyses: 6-fold-rise added Appendix 15: details added Addition of intermediate analysis
4.0	06-Sep-2023	Updates to align with protocol V6.0 and to detailed immunogenicity strains not planned in the protocol
5.0	14-Nov-2023	Updates to align with protocol V7.0 and to change the Interim Analysis 2 scope as an interim CSR is now planned
6.0	21-Jul-2025	Updates to align with protocol V7.0. According to the schedule of activities in protocol V7.0, the time window for booster vaccination at Visit 08 in Per-protocol analysis set is updated.

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1 Overall Design

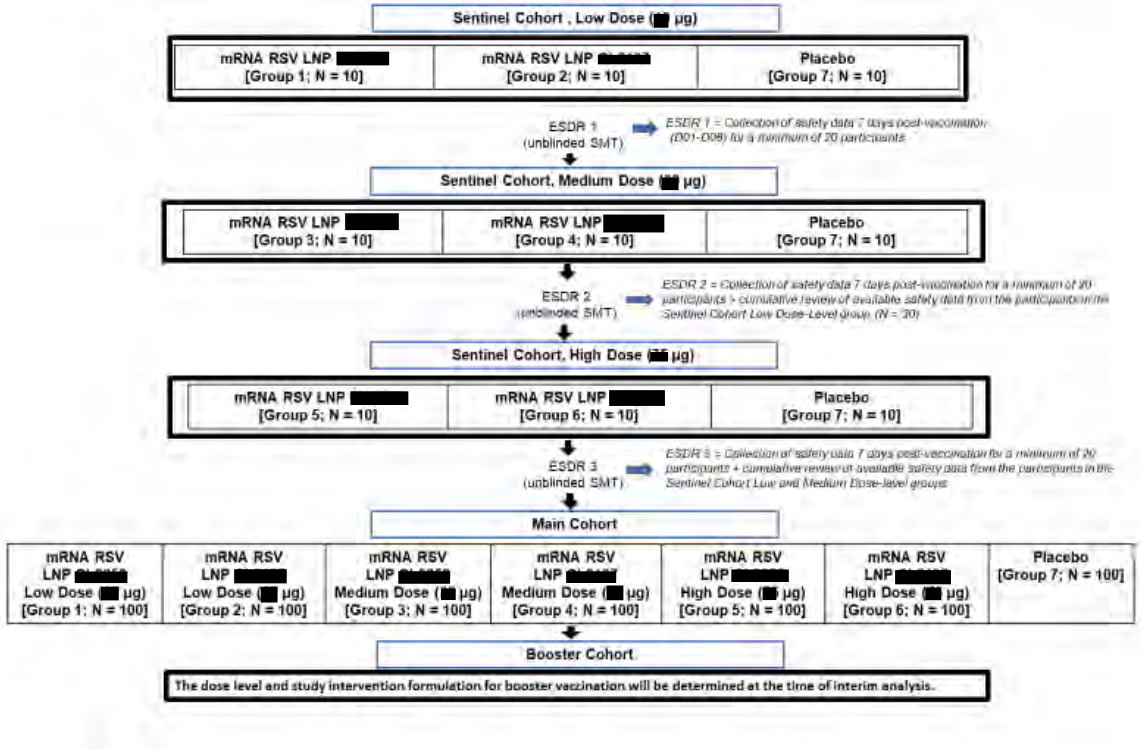
The design of the study is summarized in Table 1.1. Detailed design is provided in Sections 4.1.1 and 1.1.1 of the protocol.

Table 1.1: Overall Design

Type of design	Sequential (Phase I)/ Parallel, multi-center (Phase IIa)
Phase	I/IIa
Control method	Placebo-controlled
Study population	Healthy adults aged 18 to 50 years, and 60 years and older
Level and method of blinding	Sentinel Cohort: Single-blind • Investigators, laboratory personnel, and participants will be blinded • Sponsor study staff and study staff preparing/administering the study interventions will be unblinded • Safety data will be reviewed in an unblinded manner by the Sponsor Safety Management Team (SMT) during the Sentinel Cohort. An unblinded Sponsor SMT will perform ESDRs for each of the 3 dose-levels in the Sentinel Cohort. Main Cohort: Modified double-blind • Investigators, laboratory personnel, Sponsor study staff, and participants will be blinded. • Study staff preparing/administering the study interventions will be unblinded. • Safety data will be reviewed in a blinded manner by the Sponsor Safety Management Team (SMT) until the code is broken for the Sponsor for the planned interim analysis of the Main Cohort. Once the code is broken, safety data will be reviewed in an unblinded manner for the Booster Cohort • For the Main and Booster Cohorts, an internal Safety Evaluation Review Team (SERT), independent of the study team, will review unblinded data during the study if recommended by Safety Governance
Study intervention assignment method	Randomization
Number of participants	A total of 790 participants are planned to be randomized, with 90 participants aged 18 to 50 years in the Sentinel Cohort and 700 participants aged 60 years and older in the Main Cohort (see Table 1.2 and Table 1.3, respectively). Approximately 200 participants from the Main Cohort will be enrolled in the Booster Cohort (see Table 1.4). It is also planned for the first 140 participants enrolled in the Main Cohort to be selected for inclusion in the cell-mediated immunity (CMI) subset.

	Participants in the CMI subset will be enrolled from a limited number of selected sites.
Intervention groups	Sentinel Cohort: Enrollment of participants and dose-escalation will be performed in a stepwise manner, based on the favorable ESDRs by an internal SMT. Refer to Section 8.4.9.1 of the protocol and Figure 1.1 for details on sequential enrollment and ESDRs. Starting with the low dose formulations, and for each of the 3 dose-levels, eligible participants will be randomized in a 1:1:1 ratio to receive a single administration of RSV mRNA vaccine with LNP containing [redacted], RSV mRNA vaccine with LNP containing [redacted], or placebo (see Table 1.2) Main Cohort: Enrollment of the Main Cohort may proceed once a cumulative ESDR from the Sentinel Cohort is completed. Eligible participants will be randomized in a 1:1:1:1:1:1:1 ratio for the Main Cohort to receive a single administration of RSV mRNA vaccine with LNP containing [redacted] (low, medium, or high dose), RSV mRNA vaccine with LNP containing [redacted] (low, medium, or high dose), or placebo (see Table 1.3) Booster Cohort: Participants enrolled in the Booster Cohort will receive a booster vaccination 12 months after the first injection. Eligible participants will be selected from the placebo group (N = 100) and the selected dose group (ie, the dose level and LNP formulation selected based upon safety and immunogenicity results from the Main Cohort; N = 100) of the Main Cohort. Participants in the Booster Cohort will be randomized to receive either a booster dose of the selected formulation or placebo (see Table 1.4)
Total duration of study participation	Sentinel and Main Cohorts: 12 months Booster Cohort: 24 months (12 months post-primary vaccination + 12 months post-booster dose)
Countries	Phase I/IIa: US, Puerto Rico, Australia* (*countries may be added or removed as necessary, based on study evolution)
Use of an Independent Data Monitoring Committee, Dose-Escalation Committee, or similar review group	SMT, SERT, PSB, CAC (see Section 10.1.5 of the protocol)

Figure 1.1: Enrollment strategy



ESDR: early safety data review; LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; RSV: respiratory syncytial virus; SMT: safety management team.

Table 1.2: Planned sample size for Sentinel Cohort (participants aged 18 to 50 years)

Subcohort Number	Group	Study Intervention	Dose Level	Unit Dose (µg)	N
1	1	RSV mRNA LNP [redacted]	Low SC	[redacted]	10
	2	RSV mRNA LNP [redacted]			10
2	3	RSV mRNA LNP [redacted]	Medium SC		10
	4	RSV mRNA LNP [redacted]			10
3	5	RSV mRNA LNP [redacted]	High SC		10
	6	RSV mRNA LNP [redacted]			10
1, 2, 3	7	Placebo	N/A	N/A	30

Table 1.3: Planned sample size for Main Cohort (participants aged 60 years and older)

Group	Study Intervention	Dose Level	Unit Dose (µg)	N
1	RSV mRNA LNP [redacted]	Low	[redacted]	100
2	RSV mRNA LNP [redacted]	Low		100
3	RSV mRNA LNP [redacted]	Medium		100
4	RSV mRNA LNP [redacted]	Medium		100
5	RSV mRNA LNP [redacted]	High		100
6	RSV mRNA LNP [redacted]	High		100
7	Placebo	N/A	N/A	100

Table 1.4: Planned sample size for Booster Cohort (participants aged 60 years and older)

Group	Study Intervention	Dose Level	Unit Dose (µg)	N
6	RSV mRNA LNP [redacted]	High	[redacted]	100*
7	Placebo	N/A	N/A	100*

* N is defined here without considering the drop-out rate at the time of booster vaccination. Participants in the Booster Cohort will be randomized in a 1:1 ratio to receive either a booster dose of the selected formulation or placebo.

Table 1.5: Schedule of activities for the Sentinel Cohort (participants aged 18 to 50 years)

Phase I/IIa Study, 1 Screening Visit, 7 Planned Visits, 8 Telephone Calls, 1 Vaccination, 9 Blood Samples, 12 Months Duration Per Participant

Visit	***Collection of information in the CRF***	**Screening**	**V01**	**TC1**	**V02**	**TCs 2-4**	**V03**	**V04**	**V05**	**TCs 5-6**	**V06**	**TCs 7-8**	**V07**	**Resp. Illness Visit(s) ††**
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05 to D07 (1x/D)**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d**	**V01 + 120d, 150d**	**V01 + 179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**±1d**		**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Visit procedures:														
In-person Visit		X	X		X		X	X	X		X		X	X
Non-visit contact*				X		X				X		X		
Informed consent	*X*	X												
Inclusion/exclusion criteria	*X*	X	X											
Collection of demographic data/body stature	*X*	X												
Collection of medical history	*X Significant Medical History*	X												
Collection of vaccination history with mRNA vaccines	*X*	X												
Urine or serum pregnancy test (as determined by local regulations) if applicable			X											
Physical examination		X	X		X†		X†	X†	X†		X†		X†	
Electrocardiogram‡	*X*	X												
Pre-vaccination temperature§			X											

Visit	***Collection of information in the CRF***	**Screening**	**V01**	**TC1**	**V02**	**TCs 2-4**	**V03**	**V04**	**V05**	**TCs 5-6**	**V06**	**TCs 7-8**	**V07**	**Resp. Illness Visit(s) ††**
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05 to D07 (1x/D)**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d**	**V01 + 120d, 150d**	**V01 + 179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**±1d**		**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Allocation of participant number	*X*	X												
Randomization of participant	*X*		X											
Blood sampling (BL) for immunogenicity assay	*X*		BL0001Pre-vac					BL0002	BL0003		BL0004		BL0005	
Blood sampling (BS) for assessment of safety**	*X*	BS0001			BS0002		BS0003	BS0004						
Blood sampling for HIV, Hepatitis B, Hepatitis C serology		X												
Nasal swab††	*X*													UNXXXX‡‡‡
Vaccination (vac)	*X*		X											
Immediate surveillance (30 min) ‡‡	*X*		X											
DC provided			DC1											
DC reviewed					DC1	DC1	DC1	DC1						
DC collected								DC1						
MA provided								X						
MA reviewed									X	X	X	X	X	
Collection of solicited injection site and systemic reactions§§	*X*		7 days after vaccination											
Collection of unsolicited AEs and MAAEs§§	*X*		28 days after vaccination											
Collection of AESIs§§	*X*		Throughout the study											

Visit	*Collection of information in the CRF*	Screening	V01	TC1	V02	TCs 2-4	V03	V04	V05	TCs 5-6	V06	TCs 7-8	V07	Resp. Illness Visit(s) ††
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05 to D07 (1x/D)**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d**	**V01 + 120d, 150d**	**V01 + 179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**±1d**		**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Collection of SAEs	*X*													
Collection of concomitant medications	*X Reportable concomitant medication*	X	X		X		X	X	X***		X***		X***	
End of primary study intervention phase at D29†††	*X*							X						
End of Study	*X*												X	

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BL: blood sampling for immunogenicity; BS: blood sampling for assessment of safety; CRF: case report form; D, d: day(s); DC: diary card; M: month; MA: memory aid; MAAE: medically attended adverse events; NS: nasal swab; PRN: as needed; Resp.: Respiratory (Illness Visit); SAE: serious adverse event; TC: telephone call; ; UN: blood sampling for Illness Visit; V: visit; vac: vaccination

* Non-site visit contacts are to be made by phone at scheduled timepoints in the study; alternative methods of contact such as e-mail, text message, or other means are allowed as needed.

† Targeted physical examinations for all in-person visits after Visit 01.

‡ Electrocardiogram (ECG) to be performed at Screening as a baseline, and reviewed by investigator for features of previous myocarditis, pericarditis, and/or myopericarditis. Additional ECG will be performed as rapidly as possible (ie, at an unscheduled visit, if necessary) for any participant who develops symptoms of myocarditis, pericarditis, and/or myopericarditis during conduct of the study.

§ Temperature is to be measured by oral route (preferred) or axillary route using a standard digital thermometer and recorded in the source document.

** Safety laboratory assessments will include serum chemistries, hematology, and coagulation times (see Table 22 of the study protocol). At Screening and V03 a serum volume sample will be taken for Troponin I level testing as part of the safety laboratory assessments; part of the samples taken at V04, V05, V06, and V07 will be stored for potential future testing of Troponin I in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis (Screening blood sample will be used as baseline). In case of abnormal safety laboratory results, unscheduled visits may occur based on investigator's judgment. The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements.

†† Nasal swab specimen for the detection of RSV and other respiratory pathogens (including COVID-19) will be collected from participants during Respiratory Illness Visits including medically attended visits during the study. If a participant visits any other non-study doctor / hospital for an 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 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 on-site Illness Visit will be evaluated first by video call (preferred) or regular phone call if video call is not possible, to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

‡‡ Any unsolicited systemic AEs occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic AEs in the case report form.

§§ The participant will record information in a DC about solicited reactions, unsolicited AEs, and MAAEs from D01 to D29 after vaccine administration, and AESIs and SAEs throughout the study.

*** Only medications that may have an impact on the immune response or that may have an impact on both the safety and immune response will be collected.
††† In case of participant discontinuation at a visit, the entire visit will be completed.
‡‡‡ "X" indicates that the nasal swab number will be unique to each site. Further details are provided separately. A nasal swab for central laboratory testing will be collected. A sample for local laboratory testing (clinical care) may be collected in addition to the UN swab for central laboratory testing. The swab will not be collected during an Illness Visit if the date of collection is more than 14 days after resolution of symptoms.

Table 1.6: Schedule of activities for the Main Cohort (participants aged 60 years and older)

Phase I/IIa Study, 1 Screening Visit, 6 Planned Visits, 4 Telephone Calls, 1 Vaccination, 10 Blood Samples, 12 Months Duration Per Participant (D01 to 12 months)

Visit	*Collection of information in the CRF*	Screening	V01	V02*	V03	V04	V05	TCs 1-2	V06	TCs 3-4	V07	Resp. Illness Visit(s) §§
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D04**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 9M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval					**V01 +7d**	**V01 +28d**	**V01 +89d**	**V01 + 120d, 150d**	**V01 +179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Visit procedures:												
In-person Visit		X	X		X	X	X		X		X	X
Non-visit contact†								X		X		
Informed consent	*X*	X										
Inclusion/exclusion criteria	*X*	X	X									
Collection of demographic data/body stature	*X*	X										
Collection of medical history	*X Significant Medical History*	X										
Collection of vaccination history with mRNA vaccines	*X*	X										
Physical examination		X	X		X‡	X‡	X‡		X‡		X‡	

Visit	*Collection of information in the CRF*	Screening	V01	V02*	V03	V04	V05	TCs 1-2	V06	TCs 3-4	V07	Resp. Illness Visit(s) §§
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D04**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 9M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval					**V01 +7d**	**V01 +28d**	**V01 +89d**	**V01 + 120d, 150d**	**V01 +179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Electrocardiogram (ECG)§	*X*	X										
Pre-vaccination temperature**			X									
Allocation of participant number	*X*	X										
Randomization of participant	*X*		X									
Blood sampling (BL) for immunogenicity assay	*X*		BL0001 Pre-vac			BL0002	BL0003		BL0004		BL0005	
Blood sampling for CMI††	*X*		WB0001 Pre-vac		WB0002							
Blood sampling (BS) for assessment of safety‡‡	*X*	BS0001			BS0002	BS0003						
Blood sampling for HIV, Hepatitis B, Hepatitis C serology		X										
Nasal Swab§§	*X*											UNXXXX ****
Vaccination (vac)	*X*		X									
Immediate surveillance (30 min) ***	*X*		X									

Visit	***Collection of information in the CRF***	**Screening**	**V01**	**V02***	**V03**	**V04**	**V05**	**TCs 1-2**	**V06**	**TCs 3-4**	**V07**	**Resp. Illness Visit(s) §§**
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D04**	**D08**	**D29**	**3M**	**4M, 5M (1x/M)**	**6M**	**8M, 9M, 10M (1x/2M)**	**12M**	**PRN**
Visit Interval					**V01 +7d**	**V01 +28d**	**V01 +89d**	**V01 + 120d, 150d**	**V01 +179d**	**V01 + 239d, 299d**	**V01 + 364d**	
Time windows					**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Diary card (DC) provided			DC1									
DC reviewed					DC1	DC1						
DC collected						DC1						
MA provided						X						
MA reviewed							X	X	X	X	X	X
Collection of solicited injection site and systemic reactions†††	*X*		7 days after vaccination									
Collection of unsolicited AEs and MAAEs†††	*X*		28 days after vaccination									
Collection of AESIs†††	*X*		Throughout the study									
Collection of SAEs	*X*											
Collection of concomitant medications	*X Reportable concomitant medication*	X	X		X	X	X‡‡‡		X‡‡‡		X‡‡‡	
End of primary study intervention phase at D29§§§	*X*					X						
End of primary series at 12M											X	
End of study††††	*X*										X	

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BL: blood sampling for immunogenicity; BS: blood sampling for assessment of safety; CMI: cell-mediated immunity; CRF:case report form; D, d: Days; DC: diary card; M: month(s); MA: memory aid; MAAE: medically attended adverse event; NS: nasal swab; PRN: as needed; Resp.: Respiratory (Illness Visit); SAE: serious adverse event; TC: telephone call; UN: blood sample for Illness Visit; V: visit; vac: vaccination; WB: blood sample for TruCulture.

* Day 04 visit (V02) does not apply to the Main Cohort.

† Non-site visit contacts are to be made by phone at scheduled timepoints in the study; alternative methods of contact such as e-mail, text message, or other means are allowed as needed.

‡ Targeted physical examinations for all in-person visits after Visit 01.

§ Electrocardiogram to be performed at Screening as a baseline, and reviewed by investigator for features of previous myocarditis, pericarditis, and/or myopericarditis. Additional ECG will be performed as rapidly as possible (ie, at an unscheduled visit, if necessary) for any participant who develops symptoms of myocarditis, pericarditis, and/or myopericarditis during conduct of the study.

** Temperature is to be measured by oral route (preferred) or axillary route using a standard digital thermometer and recorded in the source document.

†† Samples collected from a subset of 140 participants for CMI assays to be assessed by TruCulture.

‡‡ Safety laboratory assessments will include serum chemistries, hematology, and coagulation times (see Table 22 of the study protocol). At Screening and at V03, a serum volume sample will be taken for Troponin I level testing as part of the safety laboratory assessments; part of the samples taken at V01, V04, V05, V06, and V07 will be stored for potential future testing of Troponin I in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis (Screening blood sample will be used as baseline). In case of abnormal safety laboratory results, unscheduled visits may occur based on investigator's judgment. The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements.

§§ Nasal swab specimen for the detection of RSV and other respiratory pathogens (including COVID-19) will be collected from participants during Respiratory Illness Visits including medically attended visits during the study. If a participant visits any other non-study doctor / hospital for an 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 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 on-site Illness Visit will be evaluated first by video call (preferred) or regular phone call if video call is not possible, to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

*** Any unsolicited systemic AEs occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic AEs in the case report form.

††† The participant will record information in a DC about solicited reactions and unsolicited AEs, and MAAEs from D01 to D29 after vaccine administration and AESIs and SAEs throughout the study.

‡‡‡ Only medications that may have an impact on the immune response or that may have an impact on both the safety and immune response will be collected.

§§§ In case of participant discontinuation at a visit, the entire visit will be completed.

**** "X" indicates that the nasal swab number will be unique to each site. Further details are provided separately. A nasal swab for central laboratory testing will be collected. A sample for local laboratory testing (clinical care) may be collected in addition to the UN swab for central laboratory testing. The swab will not be collected during an Illness Visit if the date of collection is more than 14 days after resolution of symptoms.

†††† For participants who will not continue to Booster Cohort.

Table 1.7: Schedule of activities for the Booster Cohort (participants aged 60 years and older)

Phase I/IIa Study, 1 Screening Visit, 6 Planned Visits, 4 Telephone Calls, 1 Vaccination, 7 Blood Samples, 12 Months Duration Per Participant (Month 12 to Month 24)

Visit	***Collection of information in the CRF***	**Screening V08***	**V08**	**V09**	**V10**	**V11**	**TCs 5-6**	**V12**	**TCs 7-8**	**V13**	**Resp. Illness Visit(s)** §§
Study timelines		**- D14 12M to - D01 12M**	**12M**	**12M+7d**	**12M+28d**	**15M**	**16M, 17M (1x/month)**	**18M**	**20M, 22M (1x/2M)**	**24M**	**PRN**
Visit Interval			**V01+12M (Vac2)**	**V08+7d**	**V08+28d**	**V08+89d**		**V08+179d**		**V08+364d**	
Time windows			**V07+14d**	**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Visit procedures:											
In-person Visit		X	X	X	X	X		X		X	X
Non-visit contact†							X		X		
Physical examination		X	X	X‡	X‡	X‡		X‡		X‡	X‡
Collection of vaccination history with mRNA vaccines	*X*	X									
Electrocardiogram (ECG)§	*X*	X									
Pre-vaccination temperature**			X								
Temporary and definitive contraindications	*X*		X								
Randomization	*X*		X								

Visit	*Collection of information in the CRF*	Screening V08*	V08	V09	V10	V11	TCs 5-6	V12	TCs 7-8	V13	Resp. Illness Visit(s) §§
Study timelines		**- D14 12M to - D01 12M**	**12M**	**12M+7d**	**12M+28d**	**15M**	**16M, 17M (1x/month)**	**18M**	**20M, 22M (1x/2M)**	**24M**	**PRN**
Visit Interval			**V01+12M (Vac2)**	**V08+7d**	**V08+28d**	**V08+89d**		**V08+179d**		**V08+364d**	
Time windows			**V07+14d**	**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Visit procedures:											
Blood sampling (BL) for Immunogenicity assay††	*X*				BL0006	BL0007		BL0008		BL0009	
Blood sampling (BS) for assessment of safety‡‡	*X*	BS0001A		BS0002A	BS0003A						
Blood sampling for HIV, Hepatitis B, Hepatitis C serology		X									
Nasal swab§§	*X*										UNXXXX****
Vaccination (vac)	*X*		X***								
Immediate surveillance (30 min)†††	*X*		X								
Diary card (DC) provided			DC2								
DC reviewed				DC2	DC2						
DC collected					DC2						
Memory Aid (MA) provided					X						
MA reviewed						X	X	X	X	X	X
Collection of solicited injection site and systemic reactions‡‡‡	*X*		7 days after vaccination								

Visit	*Collection of information in the CRF*	Screening V08*	V08	V09	V10	V11	TCs 5-6	V12	TCs 7-8	V13	Resp. Illness Visit(s) §§
Study timelines		**- D14 12M to - D01 12M**	**12M**	**12M+7d**	**12M+28d**	**15M**	**16M, 17M (1x/month)**	**18M**	**20M, 22M (1x/2M)**	**24M**	**PRN**
Visit Interval			**V01+12M (Vac2)**	**V08+7d**	**V08+28d**	**V08+89d**		**V08+179d**		**V08+364d**	
Time windows			**V07+14d**	**+1d**	**+7d**	**+14d**		**+14d**		**+28d**	
Visit procedures:											
Collection of unsolicited AEs and MAAEs‡‡‡	*X*		28 days after vaccination								
Collection of SAEs and AESIs‡‡‡	*X*		Throughout the study								
Collection of concomitant medications	*X Reportable concomitant medication*	X	X	X	X	X§§§		X§§§		X§§§	
End of study participation										X	

Abbreviations: AE: adverse events; AESI: adverse event of special interest; BL: blood sampling for immunogenicity; BS: blood sampling for assessment of safety; CRF: case report form; D, d: day; DC: diary card; M: month; MA: memory aid; MAAE: medically attended adverse event; NS: nasal swab; PRN: as needed; Resp.: Respiratory (Illness Visit); SAE: serious adverse event; TC: telephone call; UN: blood sample for Illness Visit; V: visit; vac: vaccination; Vac2: booster vaccination.

* The screening visit for the Booster Cohort may take place on the same day as the 12-month Main Cohort follow-up visit (ie, V07).

† Non-site visit contacts are to be made by phone at scheduled timepoints in the study; alternative methods of contact such as e-mail, text message, or other means are allowed as needed.

‡ Targeted physical examinations for all in-person visits after Visit 08. Temperature is to be measured by oral route (preferred) or axillary route using a standard digital thermometer and recorded in the source document.

§ Electrocardiogram (ECG) to be performed at Screening as a baseline, and reviewed by investigator for features of previous myocarditis, pericarditis, and/or myopericarditis. Additional ECG will be performed as rapidly as possible (ie, at an unscheduled visit, if necessary) for any participant who develops symptoms of myocarditis, pericarditis, and/or myopericarditis during conduct of the study.

** Temperature is to be measured by oral route (preferred) or axillary route using a standard digital thermometer and recorded in the source document.

†† BL0005, obtained at V07, will be used as the pre-vaccination sample in the Booster Cohort.

‡‡ Safety laboratory assessments will include serum chemistries, hematology, and coagulation times (see Table 22 of the study protocol). At Screening and at V09, a serum volume sample will be taken for Troponin I level testing as part of the safety laboratory assessments; part of the samples taken at V10, V11, V12, and V13 will be stored for potential future testing of Troponin I in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis (Screening blood sample will be used as baseline). In case of abnormal safety laboratory results, unscheduled visits may occur based on investigator's judgment. The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements.

§§ Nasal swab specimen for the detection of RSV and respiratory pathogens (including COVID-19) will be collected from participants during Respiratory Illness Visits including medically attended visits during the study. If a participant visits any other non-study doctor / hospital for an 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 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 on-site Illness Visit will be evaluated first by video call (preferred) or regular phone call if video call is not possible, to enable remote evaluation of severity and remote management of mild (Grade 1) illness, as deemed appropriate by the study investigator.

*** To be administered 12 months after the first injection.

††† Any unsolicited systemic AEs occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic AEs in the case report form.

‡‡‡ The participant will record information in a DC about solicited reactions, unsolicited AEs, and MAAEs from D01 to D29 after vaccine administration and AESIs and SAEs throughout the study.

§§§ Only medications that may have an impact on the immune response or that may have an impact on both the safety and immune response will be collected.

**** "X" indicates that the nasal swab number will be unique to each site. Further details are provided separately. A nasal swab for central laboratory testing will be collected. A sample for local laboratory testing (clinical care) may be collected in addition to the UN swab for central laboratory testing. The swab will not be collected during an Illness Visit if the date of collection is more than 14 days after resolution of symptoms.

2 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Primary	
Safety Objective To assess the safety profile of 3 different dose-levels of RSV mRNA vaccine candidate with an LNP containing [redacted] and RSV mRNA vaccine candidate with an LNP containing [redacted]	***Safety Endpoints*** • Presence of unsolicited systemic AEs reported in the 30 minutes after vaccination • Presence of solicited injection site and systemic reactions (ie, pre-listed in the participant's DC and in the eCRF) occurring up to 7 days after vaccination • Presence of unsolicited AEs and MAAEs reported up to 28 days after vaccination • Presence of serious AEs (SAEs), and AEs of special interest (AESIs) throughout the study • Presence of out-of-range biological test results up to 7 days after vaccination
Immunogenicity Objective To assess the immunogenicity of 3 different dose-levels of RSV mRNA vaccine candidate encapsulated in an LNP containing [redacted] and RSV mRNA vaccine candidate encapsulated in an LNP containing [redacted]	***Immunogenicity Endpoint*** RSV-A serum nAb titers at pre-vaccination (D01) and 28 days post-primary vaccination (D29)
Secondary	
Safety Objective To assess safety profile of a booster vaccination given 12 months after the primary vaccination, in a subset of participants	***Safety Endpoints*** • Presence of immediate unsolicited systemic AEs reported in the 30 minutes after booster vaccination • Presence of solicited injection site and systemic reactions occurring up to 7 days after booster vaccination • Presence of unsolicited AEs and MAAEs reported up to 28 days after booster vaccination • Presence of SAEs and AESIs throughout the study • Presence of out-of-range biological test results up to 7 days after booster vaccination

Objectives	Endpoints
Immunogenicity Objectives 1) To assess the durability of immune response at 3, 6, and 12 months following primary vaccination on D01 2) To assess the durability of the immune response following booster vaccination 12 months after the primary vaccination, in a subset of participants	***Immunogenicity Endpoints*** Endpoints for objective #1: • RSV-A serum nAb titers at pre-vaccination (D01), 28 days (D29), and 3, 6, and 12 months post-primary vaccination • Serum anti-F immunoglobulin G (IgG) Ab titers at pre-vaccination (D01), 28 days (D29), and 3, 6, and 12 months post-primary vaccination Endpoints for objective #2: • RSV-A serum nAb titers at pre-booster vaccination, 28 days, and 3, 6, and 12 months post-booster vaccination • Serum anti-F IgG Ab titers at pre-booster vaccination, 28 days, and 3, 6, and 12 months post-booster vaccination
Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

3 Statistical Considerations

3.1 Statistical Hypotheses

All analyses will be descriptive. No statistical hypotheses will be tested.

3.2 Sample Size Determination

This is a first-in-human study to assess the safety profile and immune responses to different formulations of the study vaccine when compared to a placebo. No sample size calculation was done as there are no statistical hypotheses in this study.

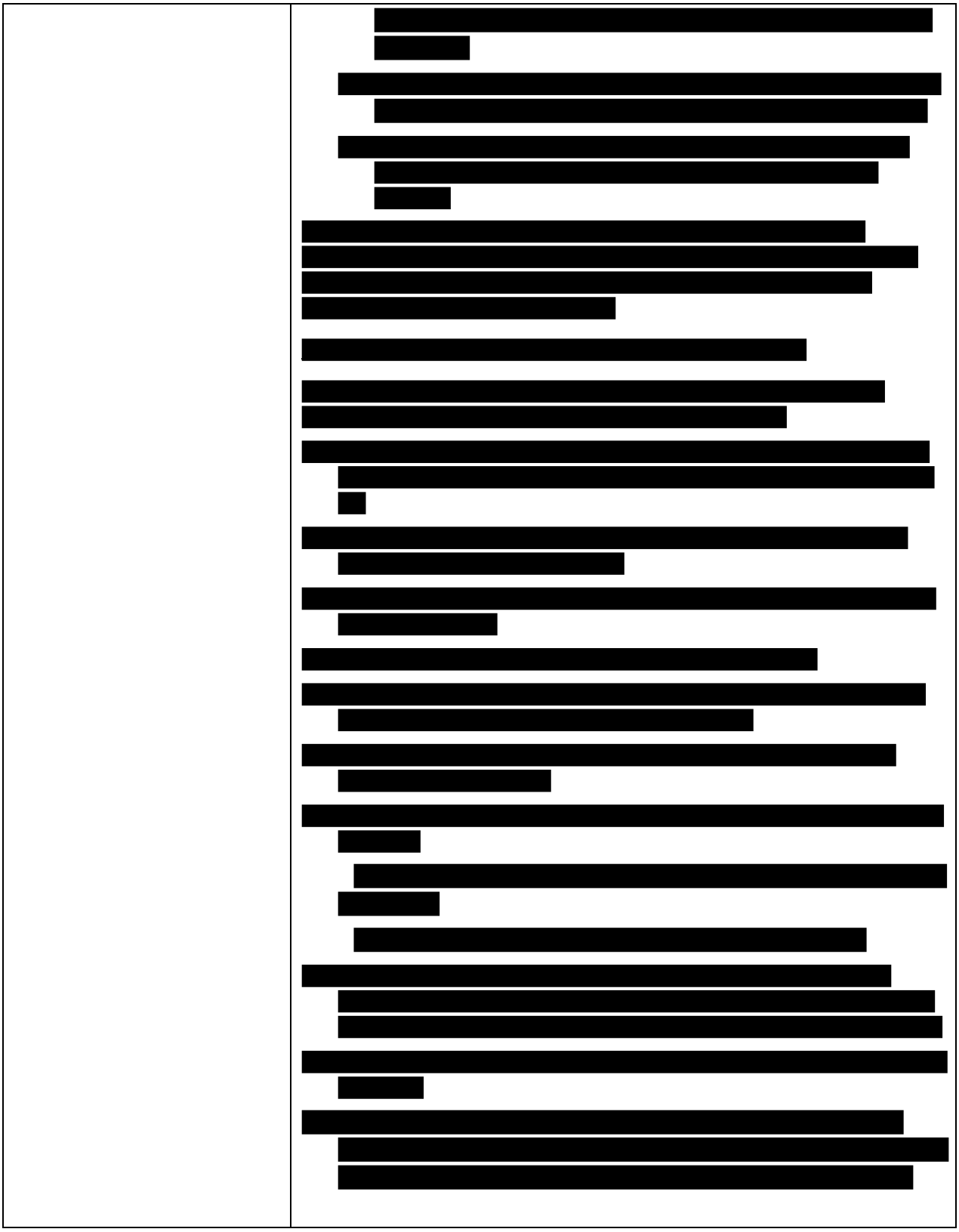
A total of 790 participants are planned to be enrolled. The sample size is arbitrarily fixed at 90 participants in the Sentinel Cohort and 700 participants in the Main Cohort (100 per study intervention group), based on clinical feasibility.

3.3 Populations for Analyses

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

Participant Analysis Set	Description
Screened Participants with eCRF	All participants with an eCRF
Randomized	All participants allocated to a study intervention group at randomization at Visit 01
Safety Analysis Set (SafAS)	Participants who have received at least 1 injection of the study vaccine or placebo. Three SafAS will be defined: one for the primary vaccination at Visit 01 (SafAS1), one for the booster vaccination at Visit 08 (SafAS2), and one for any vaccination during the entire study (Overall SafAS): • SafAS1: Participants who have received the study vaccine or placebo at Visit 01 • SafAS2: Participants who have received the booster vaccination or placebo at Visit 08 • Overall SafAS: Participants who have received at least 1 injection of the study vaccine or placebo during the entire study All participants will have their safety analyzed according to the study intervention(s) they actually received. For Overall SafAS, safety will be analyzed according to the study intervention they actually received at first and at booster injection. Safety data recorded for a study intervention received out of the protocol design will be excluded from the analysis (and listed separately).

Full analysis set (FAS)	[redacted]
Per-protocol analysis set (PPAS)	[redacted]



	[redacted]
Subpopulation for exploratory objectives	A subset of FAS1 will be used for CMI analyses (FAS1 CMI). FAS1 CMI: Subset of randomized participants who received the study vaccine or placebo at Visit 01 among the 140 participants included in the CMI subset.

3.4 Statistical Analyses

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

According to the analysis, statistical analyses will be conducted by Sentinel Cohort (Sentinel Cohort 1, 2, 3), for the 3 Sentinel Cohorts pooled, for the Main Cohort and for the Sentinel and Main cohorts pooled (from D01 to 12M after the primary vaccination). Results will be presented by study intervention group, and by LNP. Analyses that will focus on booster vaccination will be conducted only on Booster Cohort (12 months following booster vaccination) by group at both V01 and V08. This will be detailed in the TLF part.

Safety analyses will be performed on the appropriate SafAS (SafAS1 for the primary vaccination, SafAS2 for the booster vaccination, Overall SafAS for any vaccination). Immunogenicity analyses will be performed on PPAS (PPAS1 for the primary vaccination, PPAS2 for the booster vaccination). If the difference between PPAS1 (respectively PPAS2) and FAS1 (respectively FAS2) is greater than 10%, a supplemental analysis based on FAS1 (respectively FAS2) will be performed to evaluate consistency of the results.

3.4.1 General Considerations

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

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

		Parameters
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 AE: Number and percentage (95% CIs) of participants. Unsolicited AE: Number and percentage (95% CIs) of participants and number of events. Illness events: Number and percentage (95% CIs) of participants and number of events.
Biological safety results	**Categorical data**	Number and percentage (95% CIs) of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum
Immunogenicity 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).
Cellular immunity results	**Categorical data**	Detailed in an exploratory SAP
	Continuous data	

[redacted]

[redacted]

3.4.2 Primary Endpoints

3.4.2.1 Safety

The safety endpoints after the primary vaccination will be summarized by study group and described by frequencies and 95% CI using the exact binomial method (Clopper-Person method).

Safety analyses will include but are not limited to the following descriptions listed in Table 3.2:

Table 3.2: Statistical analyses for clinical safety objectives

Endpoint	Time	Description
Immediate unsolicited systemic AEs/ARs	Within 30 minutes after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest.
Solicited reactions: - solicited injection site reaction - solicited systemic reaction	Within 7 days after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest, and according to: - presence - time period - time of onset - maximum intensity - number of days of occurrence - action taken and discontinuation
Unsolicited AEs/ARs	Within 28 days after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of AEs/ARs, and according to: - maximum intensity - time of onset - duration - System Organ Class (SOC) and Preferred term (PT)
Grade 3 Unsolicited AEs/ARs	Within 28 days after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of AEs/ARs, and according to SOC and PT
MAAEs	Within 28 days after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of all and related MAAEs, and according to SOC and PT.
AESIs	Within 28 days after each vaccination During the primary series (ie up to 12M after primary vaccination) During the booster study intervention phase (ie up to 12M	Summary Frequency Table presenting the number of participants experiencing the endpoint of interest as well as the number of AESIs. For the primary series period, for the booster study intervention phase, and for the entire study, Summary Frequency Table on all and related AESIs will be presented by SOC and PT.

	after booster vaccination) During the entire study (ie up to 24M after primary vaccination)	
SAEs	Within 28 days after each vaccination During the primary series (ie up to 12M after primary vaccination) During the booster study intervention phase (ie up to 12M after booster vaccination) During the entire study (ie up to 24M after primary vaccination)	Summary Frequency Table presenting the number of participants experiencing the endpoint of interest as well as the number of SAEs. For the primary series period, for the booster study intervention phase, and for the entire study, Summary Frequency Table will be presented according to: - seriousness criteria - outcome - and for all and related SAEs, by SOC and PT
AEs/ARs/SAEs leading to discontinuation	Within 28 days after each vaccination During the primary series (ie up to 12M after primary vaccination) During the booster study intervention phase (ie up to 12M after booster vaccination)	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of AEs/ARs/SAEs. For the primary series period and for the booster study intervention phase, Summary Frequency Table will be presented by SOC and PT.

In addition, biological safety will be analyzed by study intervention group and by LNP, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) in general and according to severity grades. Biological safety will be analyzed at Screening visit, Visit 02[a], Visit 03 and Visit 04 for Sentinel and Main Cohorts, and at Screening before Visit 08, Visit 09 and Visit 10 for Booster Cohort.

[a] Only for Sentinel Cohort

3.4.2.2 Immunogenicity

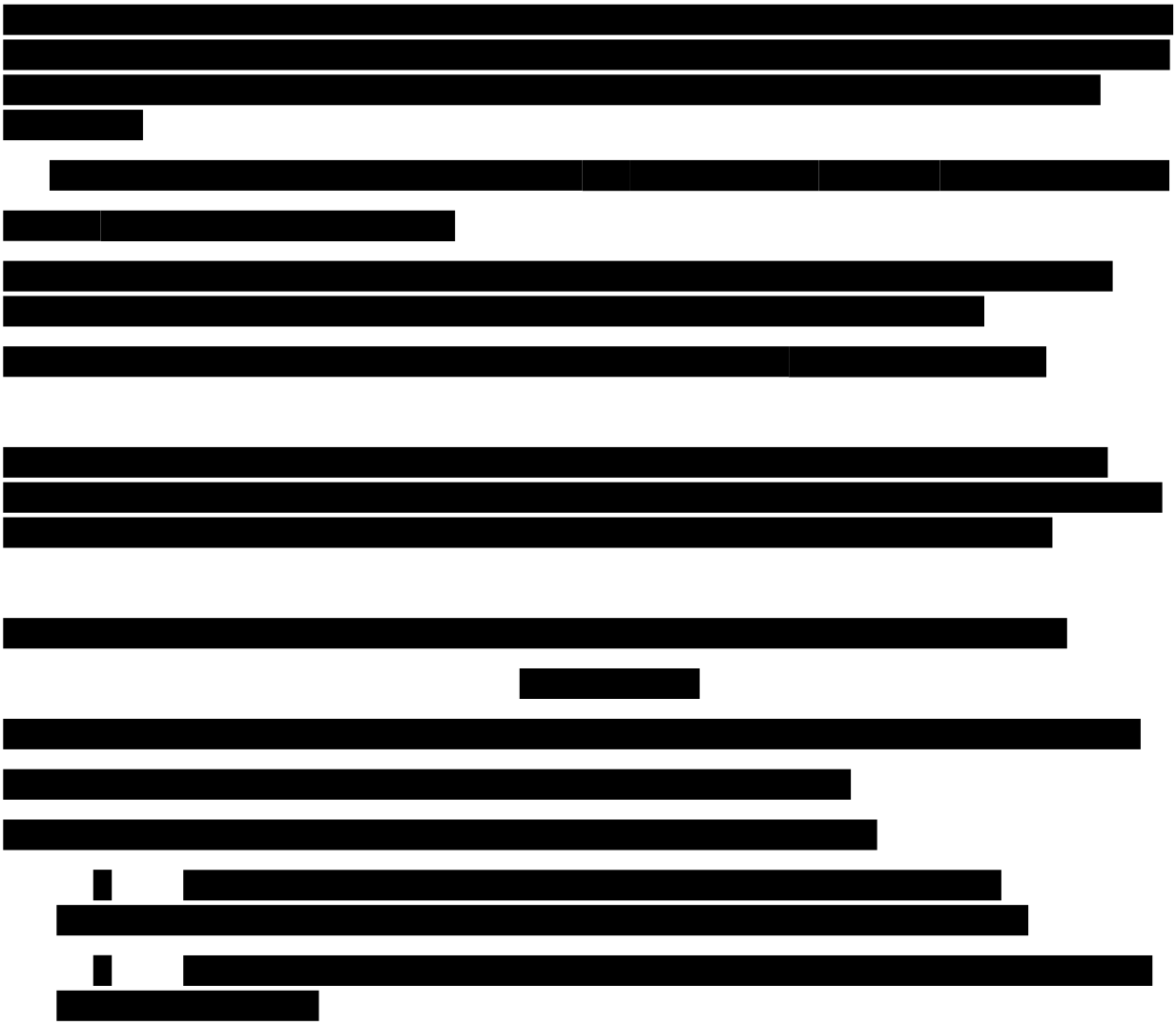
The immunogenicity endpoints for the primary vaccination (RSV-A serum nAb titers) will be summarized by study intervention group and by LNP through the following parameters:

- GMT at D01 and D29, and 95% CI (as described in Section 3.4.1)
- GMT ratio (GMTR), i.e. post-vaccination titers at D29/pre-vaccination titers at D01, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)
- Percentages of participants with titers above predefined thresholds at D29, and 95% CI (using Clopper-Pearson method)
- Seroresponse rates, ie percentages of participants achieving several X-fold from pre- to post-vaccination at D29 (4-fold, 6-fold, 8-fold, 10-fold rise), and 95% CI (using Clopper-Pearson method)
- Reverse cumulative distribution curves (RCDCs) at D01 and D29

Pairwise comparisons between groups may be estimated:

- Ratio of GMT between 2 groups (any RSV formulation vs placebo), i.e. post-vaccination titers at D29 in one RSV group/post-vaccination titers at D29 in placebo group, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)

- Difference of seroresponse rates between 2 groups (any RSV formulation vs placebo), i.e. seroresponse rate at D29 in one RSV group - seroresponse rate at D29 in placebo group, and 95% CI (using Wilson Score method without continuity correction)



3.4.3 Secondary Endpoints

3.4.3.1 Safety

The safety endpoints after the booster vaccination will be summarized by study group and described by frequencies and 95% CI using the exact binomial method (Clopper-Person method).

Safety analyses will include but are not limited to the descriptions listed in Table 3.2.

3.4.3.2 Immunogenicity

The immunogenicity endpoints for primary and booster vaccination (RSV-A serum nAb titers and RSV F IgG Ab titers) will be summarized by study intervention group and by LNP through the following parameters:

- GMT at pre-vaccination, 28 days, 3M, 6M and 12M following each vaccination, and 95% CI (as described in Section 3.4.1)
- GMT ratio (GMTR) for each vaccination, i.e. post vaccination titers 28 days, 3M, 6M and 12M following vaccination relative to pre-vaccination titers, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)
- Percentages of participants with titers above predefined thresholds 28 days, 3M, 6M and 12M following each vaccination, and 95% CI (using Clopper-Pearson method)
- Seroresponse rates after each vaccination, ie percentages of participants achieving several X-fold from pre- to post-vaccination 28 days following vaccination, 3M, 6M and 12M (4-fold, 6 fold, 8-fold, 10-fold rise)
- Reverse cumulative distribution curves (RCDCs) at pre-vaccination and 28 days post vaccination
- Boxplot of titers at pre-vaccination, 28 days, 3M, 6M and 12M following each vaccination

3.4.4 Exploratory Endpoints

3.4.4.1 Immunogenicity

Exploratory immunogenicity endpoints for primary and booster vaccination will be detailed in an exploratory SAP.

3.4.4.2 Safety

Acute Respiratory Diseases (ARD) and Lower Respiratory Tract Disease (LRTD) associated or not with RSV will be summarized for each period (after primary vaccination and after booster vaccination) by using frequencies and 95% CI (using Clopper-Pearson method).

If more than 10 cases are observed on the considered period (and with at least 1 case in the placebo group), a relative risk (RR) and its 95% CI could be computed. For the primary series, all RSV study intervention groups will be pooled and analyzed compared with placebo. For the booster study intervention phase, the selected RSV formulation will be compared with placebo.

The relative risk is defined as follow:

$$RR = (C_{RSV}/N_{RSV}) / (C_{placebo}/N_{placebo})$$

where C_{RSV} = number of cases reported in RSV group

N_{RSV} = number of participants in RSV group

$C_{placebo}$ = number of cases reported in placebo group

$N_{placebo}$ = number of participants in placebo group

95% CI could be computed using Wald method.

3.4.5 Other Safety Analyses

No other Safety Analyses will be planned.

3.4.6 Other Analyses

Subgroup analyses:

Additional analyses will be performed:

- safety and immunogenicity analyses on Japanese origin participants (if enough Japanese origin participants)
- immunogenicity analyses according to gender
- immunogenicity analyses according to age group (3 categories: 18-50 years old, 60-79 years old and 80 years old and above).

All these subgroup analyses will be performed on the appropriate FAS (FAS1 or FAS2).

COVID-19:

Impact of COVID-19 pandemic on study conduct and disposition of participants impacted by COVID-19 pandemic situation will be summarized in tables on all participants and by age group and listed in Appendix 16 of the CSR.

If more than 10% of randomized participants are impacted by COVID-19, and still evaluable for immunogenicity/safety timepoints, additional analyses in impacted/non-impacted participants will be done on main immunogenicity and safety endpoints.

3.4.7 Handling of Missing Data and Outliers

3.4.7.1 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

3.4.7.1.1 Immediate

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

3.4.7.1.2 Causal Relationship

By convention, all events reported at the injection 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 CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.7.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.7.1.4 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 3.2.1.2.3). 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.

3.4.7.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.7.2 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 4.2.4.1.

3.5 Sequence of Analyses

A first interim statistical analysis of all safety data collected up to D29 and immunogenicity data obtained at D01 and D29 will be conducted once data are available on all participants from the Sentinel Cohort. [redacted] Analyses will be performed on Sentinel Cohort only.

A second interim statistical analysis of all safety data collected up to D29 and immunogenicity data obtained at D01 and D29 will be conducted sequentially until all data are available on all participants from the Main Cohort. [redacted] Analyses will be performed on both Sentinel and Main Cohorts.

A third interim statistical analysis of all safety data and immunogenicity data collected up to M12 will be conducted once data are available on all participants from the Main Cohort. Analyses will be performed on both Sentinel and Main Cohorts.

A final analysis will be conducted once all data have been collected and the final database lock has occurred.

For exploratory objectives, the acquisition of data is flexible, and therefore, timing of the analyses will also be flexible and planned during the study at any needed time.

3.6 Data Monitoring Committee (DMC)

No DMC is planned.

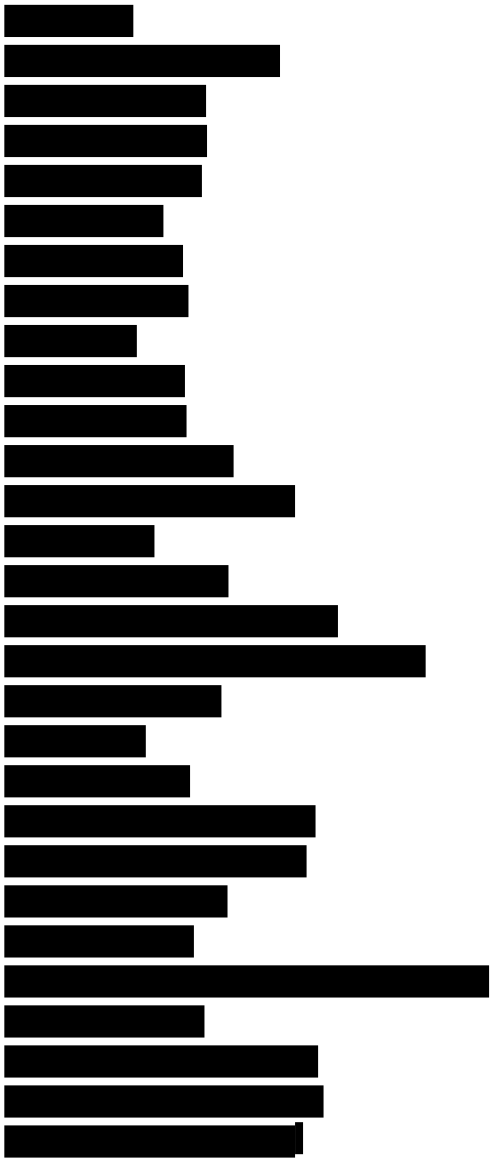
4 Complementary Information on Assessment Methods

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

4.1 Complementary Information for Endpoint Assessment Method

Acute Respiratory Disease		
Lower Respiratory Tract Disease		

For exploratory objective related to frequency of ARD and LRTD, the following list of symptoms collected will be used.



A diagnosis of RSV or other pathogens ARD or LTRD requires the documentation of any of the symptoms listed above, associated with a nasal swab positive for RSV by RT-PCR (GenMarkDx assay).

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Clinical Safety

4.2.1.1 Solicited Reactions

Table 4.1 and Table 4.2 present, respectively, the solicited injection site reactions and systemic reactions that are prelisted in the diary cards, with the intensity scales.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales – adolescents and adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.
* For pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales – children aged 2 through 11 years, adolescents, or adults aged ≥ 12 years

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia (only new or worsened)**	**Arthralgia (only new or worsened)**	**Chills**
Diary card term	Temperature	Headache	Feeling unwell/tired	Muscle aches and pains	Joint pain	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	New or worsened muscle pain. Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	New or worsened pain in a joint or joints	Sensation of cold

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia (only new or worsened)**	**Arthralgia (only new or worsened)**	**Chills**
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia (only new or worsened)**	**Arthralgia (only new or worsened)**	**Chills**
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

4.2.1.1.1 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).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as “No” and with all daily records missing (Unknown) then all daily intensities will be derived as None.

2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

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

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or 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 and later.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

Time of onset period is displayed as, D01-D04, D05-D08.

4.2.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.2.1.1.6 Overall Number of Days of Occurrence

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), the overall number of days of presence will be considered as Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 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.

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

4.2.1.2 Unsolicited AEs

4.2.1.2.1 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.

4.2.1.2.2 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 of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

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

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

4.2.1.2.3 Last Vaccination

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

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.2.1.2.4 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 4.2.1.2.3:

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

The time of onset is considered 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, 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, so will be included in these tables.

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

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

4.2.1.2.5 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.

4.2.1.2.6 Medically-Attended Adverse Event

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

4.2.1.2.7 Serious Adverse Events

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

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

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

4.2.1.2.8 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.

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

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

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.3 Seriousness

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

4.2.2.4 Outcome

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

4.2.2.5 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 3.4.7.1.2. Relationship to study procedure is only presented in the listing.

4.2.2.6 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, 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.

4.2.3 Biological Safety

Initial laboratory data are transformed into normalized results in the study data tabulation model (SDTM), via clinical data management tool.

For the computation of descriptive statistics on safety biological parameters, a normalized value X reported as:

- "< X" or "≤X" will be computed as X/2
- ">X" or "≥X" will be computed as X

Normal range determination ("within normal range" or "below/above normal range") and grading are done based on the normalized results. Normalized results will also be used for quantitative analyses.

In addition, intensity thresholds for laboratory abnormalities will be derived, as detailed in Table 4.3 (which is adjusted from Table 28 of the protocol to avoid gaps in the thresholds between two grades). The derivation is based on normalized results.

Table 4.3: Precisions for the derivation of the intensity thresholds for laboratory abnormalities

Laboratory Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Female) Absolute value – gm/dL	10.9 < value ≤ 12.0	9.4 < value ≤ 10.9	≤ 9.4
Hemoglobin (Female) change from baseline value (post value - baseline value) – gm/dL	-1.5 ≤ value < 0	- 2.0 ≤ value < -1.5	< -2.0
Hemoglobin (Male) Absolute value – gm/dL	12.4 < value ≤ 13.5	10.4 < value ≤ 12.4	≤ 10.4
Hemoglobin (Male) change from baseline value (post value - baseline value) – gm/dL	-1.5 ≤ value < 0	- 2.0 ≤ value < -1.5	< -2.0
Increase in WBC – cell/mm^3	10 800 ≤ value ≤ 15 000	15 000 < value ≤ 20 000	> 20 000
Decrease in WBC – cell/mm^3	2500 ≤ value ≤ 3500	1500 ≤ value < 2500	< 1500
Decrease in absolute Lymphocytes – cell/mm^3	750 ≤ value ≤ 1000	500 ≤ value < 750	< 500
Decrease in absolute Neutrophils – cell/mm^3	1500 ≤ value ≤ 2000	1000 ≤ value < 1500	< 1000
Eosinophils – cell/mm^3	650 ≤ value ≤ 1500	1500 < value ≤ 5000	> 5000
Decrease in Platelets – cell/mm^3	125 000 ≤ value ≤ 140 000	100 000 ≤ value < 125 000	< 100 000
PT – increase by factor (prothrombin time)	1.00 x ULN ≤ value < 1.11 x ULN	1.11 x ULN ≤ value ≤ 1.20 x ULN	>1.20 x ULN
PTT – increase by factor (partial thromboplastin time)	1.00 x ULN ≤ value <1.21 x ULN	1.21 x ULN ≤ value ≤ 1.40 x ULN	> 1.40 x ULN
Sodium – Hyponatremia - mEq/L	132 ≤ value ≤ 134	130 ≤ value < 132	< 130
Sodium – Hypernatremia - mEq/L	144 ≤ value ≤ 145	145 < value ≤ 147	> 147
Potassium – Hypokalemia - mEq/L	3.5 ≤ value ≤ 3.6	3.3 ≤ value < 3.5	< 3.3
Potassium – Hyperkalemia - mEq/L	5.1 ≤ value ≤ 5.2	5.2 < value ≤ 5.4	> 5.4
Glucose – Random - mg/dL	110 ≤ value ≤ 125	125 < value ≤ 200	> 200
BUN - mg/dL	23 ≤ value ≤ 26	26 < value ≤ 31	> 31

Laboratory Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Creatinine – mg/dL	1.5 ≤ value ≤ 1.7	1.7 < value ≤ 2.0	> 2.0
Calcium – Hypocalcemia – mg/dL	8.0 ≤ value ≤ 8.4	7.5 ≤ value < 8.0	< 7.5
Calcium – Hypercalcemia – mg/dL	10.5 ≤ value ≤ 11.0	11.0 < value ≤ 11.5	> 11.5
Total Protein – Hypoproteinemia - g/dL	5.5 ≤ value ≤ 6.0	5.0 ≤ value < 5.5	< 5.0
Alkaline phosphate – increase by factor	1.1 x ULN ≤ value < 2.1 x ULN	2.1 x ULN ≤ value ≤ 3.0 x ULN	> 3.0 x ULN
ALT (increase by factor)	1.1 x ULN ≤ value < 2.6 x ULN	2.6 x ULN ≤ value ≤ 5.0 x ULN	> 5.0 x ULN
AST (increase by factor)	1.1 x ULN ≤ value < 2.6 x ULN	2.6 x ULN ≤ value ≤ 5.0 x ULN	> 5.0 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test; increase by factor	1.1 x ULN ≤ value < 1.26 x ULN	1.26 x ULN ≤ value ≤ 1.5 x ULN	> 1.5 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 x ULN ≤ value < 1.6 x ULN	1.6 x ULN ≤ value ≤ 2.0 x ULN	> 2.0 x ULN

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal; WBC, white blood cell, LLN, lower limit of normal

4.2.4 Immunogenicity

4.2.4.1 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

4.2.4.2 Seroprotection

Not applicable.

4.2.4.3 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.

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

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

4.2.4.4 Seroconversion

Not applicable

4.2.5 Efficacy

Not applicable

4.2.6 Derived Other Variables

4.2.6.1 Age for Demographics

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

4.2.6.2 Duration of a Participant in the Trial

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

4.2.6.3 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 screening) +1.

5 Changes in the Conduct of the Trial or Planned Analyses

Due to a problem from the GCI vendor, two different strains for RSV-A are available: A2 and Long. For the second interim analysis, it was decided to produce both of them for immunogenicity outputs. After that, only the chosen one will be displayed in the outputs.

As ARD and LRTD definitions were not clearly identified for Stage 1, it was decided that exploratory objectives and endpoints about these (4), 5), and 8), 9) in Table 2.1) will be analyzed jointly.

For the second interim analysis, as 6-month follow-up safety data will be available, they will be added in the scope of the analysis.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
DMC	Data Monitoring Committee
FAS	Full analysis set
GCI	Global Clinical Immunology
GM	Geometric mean
GMT	Geometric mean of titer
IMP	Investigational Medicinal Product
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NC	Not computed
NIMP	Non- Investigational Medicinal Product
PPAS	Per-protocol analysis set
PRNT	Plaque Reduction Neutralization Test
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SOC	(Primary) System organ class
PT	Preferred term
TLF	Tables, listings and figures
ULOQ	Upper level of quantitation

7 References

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

SAP Core Body for Stage 2

Title: A Phase I/IIa, randomized, placebo-controlled multi-arm dose-finding study to evaluate the safety and immunogenicity of a RSV mRNA vaccine candidate in adult participants 18 to 50 years of age in Phase I, and 60 years and older in Phase IIa

Study Code: VAE00010

Study Phase: Phase I/IIa

SAP Core Body Version: 2.0

SAP Core Body Date: 16NOV2023

Protocol Version Number: 7.0

The SAP Code Body should be used in conjunction of the study protocol (Stage 2) and the SAP TLF for Stage 2.

Version History

Previous Version(s)	Date	Comments
1.0	04 October 2023	*First version*
2.0	16 November 2023	*Revision of Stage 2 from a Phase IIb/III seamless expansion design to Phase IIa dose-ranging design to evaluate an mRNA vaccine dose of [redacted] µg encapsulated in the LNP selected in the course of Stage 1.*

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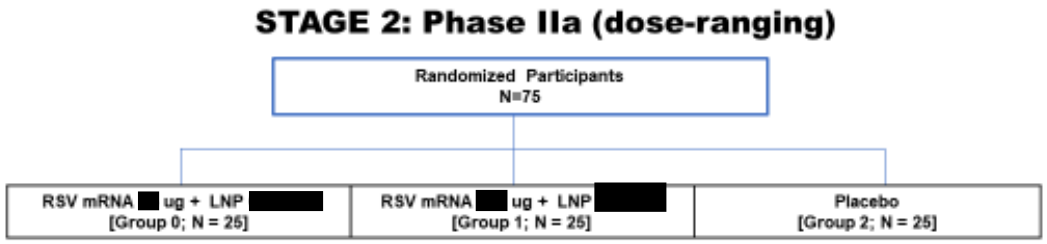
1 Overall Design

The design of the study is summarized in Table 1.1**.** Detailed design is provided in Sections 4.1.2 and 1.1.2 of the protocol.

Table 1.1: Overall design

Type of design	Phase IIa parallel, multi-center, dose-ranging
Phase	IIa
Control method	Placebo-controlled
Study population	Adults aged 60 years and older
Level and method of blinding	Modified double-blind: • Study participants, Investigators and study site staff, and Sponsor's laboratory personnel will be blinded • Study site staff preparing/administering the study interventions and Sponsor staff (excluding the laboratory personnel) will be unblinded
Investigational intervention assignment method	Randomization
Number of participants	A total of 75 participants (25 participants per arm) are planned to be randomized (see Table 1.2)
Intervention groups	For Stage 2, eligible participants will be enrolled in a 1:1:1 ratio to receive a single IM administration of the RSV mRNA vaccine candidates or placebo
Total duration of study participation	Approximately 6 months for participants
Countries	US* (*countries may be added or removed as necessary, based on study evolution)
Use of an Independent Data Monitoring Committee, Dose-Escalation Committee, or similar review group	SMT, CAC

Figure 1.1: Enrollment strategy



LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; RSV: respiratory syncytial virus.

Table 1.2: Planned sample size (participants aged 60 years and older)

Group	Study Intervention	Unit Dose (µg)	N
0	RSV mRNA + LNP [redacted]	[redacted] g	25
1	RSV mRNA + LNP [redacted]	[redacted] µg	25
2	Placebo	N/A	25

Table 1.3: Schedule of activities for the Phase IIa dose-ranging (participants aged 60 years and older)

Phase IIa Dose-Ranging Study, 1 Screening Visit, 4 Planned Visits, 8 Telephone Calls, 1 Vaccination, 6 Blood Samples, 6 Months Duration Per Participant

Visit	*Collection of information in the CRF*	Screening	V01	TC1	V02	TCs 2-4	V03	V04	TCs 5-8	End of Study
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05, D06, D07 (1x/D)**	**D08**	**D29**	**3M, 4M, 5M, 6M (1x/M)**	**6M**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 5d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d, 120d, 150d, 179d**	**V01 + 179d**
Time windows					**±1d**		**±1d**	**+7d**		
Visit procedures:										
In-person Visit		X	X		X		X	X		
Non-visit contact*				X		X			X	
Informed consent	*X*	X								
Inclusion/exclusion criteria	*X*	X	X							
Collection of demographic data/body stature	*X*	X								
Collection of medical history	*X* *Significant Medical History*	X								
Collection of vaccination history with mRNA vaccines	*X*	X								
Physical examination		X	X		X†		X†	X†		
Electrocardiogram‡	*X*	X								
Pre-vaccination temperature§			X							
Allocation of	*X*	X								

Visit	***Collection of information in the CRF***	**Screening**	**V01**	**TC1**	**V02**	**TCs 2-4**	**V03**	**V04**	**TCs 5-8**	**End of Study**
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05, D06, D07 (1x/D)**	**D08**	**D29**	**3M, 4M, 5M, 6M (1x/M)**	**6M**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 5d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d, 120d, 150d, 179d**	**V01 + 179d**
Time windows					**±1d**		**±1d**	**+7d**		
participant number										
Randomization of participant	*X*		X							
Blood sampling (BL) for immunogenicity assay	*X*		BL0001 Pre-vac					BL0002		
Blood sampling (BS) for assessment of safety**	*X*	BS0001			BS0002		BS0003	BS0004**		
Blood sampling for HIV, Hepatitis B, Hepatitis C serology		X								
Vaccination (vac)	*X*		X							
Immediate surveillance (30 min) ††	*X*		X							
DC provided			DC							
DC reviewed					DC	DC	DC	DC		
DC collected								DC		
MA provided								X		
MA reviewed									X	
Collection of solicited injection site and systemic reactions‡‡	*X*		7 days after vaccination							
Collection of unsolicited AEs‡‡	*X*		28 days after vaccination							
Collection of MAAEs‡‡	*X*		Throughout the study							

Visit	*Collection of information in the CRF*	Screening	V01	TC1	V02	TCs 2-4	V03	V04	TCs 5-8	End of Study
Study timelines (days [D]/months [M])		**-D14 to -D01**	**D01**	**D02**	**D04**	**D05, D06, D07 (1x/D)**	**D08**	**D29**	**3M, 4M, 5M, 6M (1x/M)**	**6M**
Visit Interval			**V01**	**V01 + 1d**	**V01 + 3d**	**V01 + 4d, 5d, 6d**	**V01 + 7d**	**V01 + 28d**	**V01 + 89d, 120d, 150d, 179d**	**V01 + 179d**
Time windows					**±1d**		**±1d**	**+7d**		
Collection of AESIs‡‡	*X*									
Collection of SAEs‡‡	*X*									
Collection of concomitant medications***	*X Reportable concomitant medication*	X	X		X		X	X		
End of primary study intervention phase at D29†††	*X*							X		
End of Study	*X*									X

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BL: blood sampling for immunogenicity; BS: blood sampling for assessment of safety; CRF: case report form; D, d: day(s); DC: diary card; M: month; MA: memory aid; MAAE: medically attended adverse events; NS: nasal swab; PRN: as needed; Resp.: Respiratory (Illness Visit); SAE: serious adverse event; TC: telephone call; ; UN: blood sampling for Illness Visit; V: visit; vac: vaccination

* Non-site visit contacts are to be made by phone at scheduled timepoints in the study.

† Targeted physical examinations for all in-person visits after Visit 01.

‡ Electrocardiogram (ECG) to be performed at Screening as a baseline, and reviewed by investigator for features of previous myocarditis, pericarditis, and/or myopericarditis. Additional ECG will be performed as rapidly as possible (ie, at an unscheduled visit, if necessary) for any participant who develops signs or symptoms suggestive of myocarditis, pericarditis, and/or myopericarditis during conduct of the study.

§ Temperature is to be measured by oral route (preferred) or axillary route using a standard digital thermometer and recorded in the source document.

** Safety laboratory assessments will include serum chemistries and hematology (see Table 23 of the study protocol). At Screening and V02, a serum volume sample will be taken for Troponin I level testing as part of the safety laboratory assessments; part of the samples taken at V03 and V04 will be stored for potential future testing of Troponin I in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis (Screening blood sample will be used as baseline). In case of abnormal safety laboratory results, unscheduled visits may occur based on investigator's judgment. The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements. Visit 04 (D29) sample will be collected, but additional safety tests will be performed only if required.

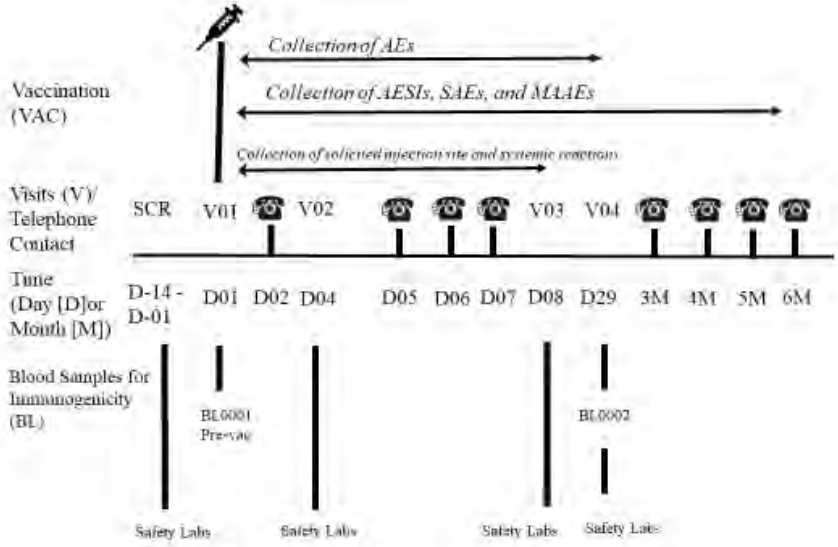
†† Any unsolicited systemic AEs occurring within the 30 minutes from vaccine administration will be recorded as immediate unsolicited systemic AEs in the case report form.

‡‡ The participant will record information in a participant diary (DC) about solicited reactions, unsolicited AEs, MAAEs, AESIs, and SAEs.

*** Only medications that may have an impact on the immune response or that may have an impact on both the safety and immune response will be collected.

††† In case of participant discontinuation at a visit, the entire visit will be completed.

Figure 1.2: Graphical study design - Phase IIa dose-ranging (participants aged 60 years and older)



AE: adverse event; AESI: adverse event of special interest; BL: blood sample; MAAE: medically attended adverse event; SAE: serious adverse event; SCR: Screening
Note: D01 (V01) blood sampling to be completed prior to vaccination.
NOTE: Visit 04 (D29) safety labs sample is for additional tests for safety purposes if required.

2 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Primary	
Safety Objective To assess the safety profile of 2 different dose-levels of RSV mRNA vaccine candidate encapsulated in an LNP containing [redacted]	***Safety Endpoints*** • Presence of unsolicited systemic AEs reported in the 30 minutes after vaccination • Presence of solicited injection site and systemic reactions (ie, pre-listed in the participant's diary and in the CRF) occurring up to 7 days after vaccination • Presence of unsolicited AEs up to 28 days after vaccination • Presence of serious AEs (SAEs), AEs of special interest (AESIs), and MAAEs throughout the study • Presence of out-of-range biological test results up to 7 days after vaccination
Immunogenicity Objective	***Immunogenicity Endpoint***
To assess the immunogenicity of 2 different dose-levels of RSV mRNA vaccine containing [redacted]	RSV A and RSV B serum nAb titers at pre-vaccination (D01) and 28 days post-primary vaccination (D29)
Secondary	
Immunogenicity Objective To assess the immune response at 28 days following vaccination on D01	***Immunogenicity Endpoints*** • Serum anti-F immunoglobulin G (IgG) Ab titers at pre-vaccination (D01) and 28 days (D29) post-vaccination

3 Statistical Considerations

3.1 Statistical Hypotheses

All analyses will be descriptive. No statistical hypotheses will be tested.

3.2 Sample Size Determination

No sample size calculation was done as there are no statistical hypotheses in this study. A total of 75 participants are planned to be enrolled. The sample size is arbitrarily fixed at 75 participants (25 per study intervention group).

3.3 Populations for Analyses

For the purposes of analysis for Phase IIa, the following analysis sets are defined:

Participant Analysis Set	Description
Screened Participants	All participants with a CRF
Randomized	All participants allocated to a study intervention group at randomization at Visit 01
Safety Analysis Set (SafAS)	Participants who have received at least 1 injection of the study vaccine or placebo at Visit 01 (SafAS3). All participants will have their safety analyzed according to the study intervention they actually received. Safety data recorded for a study intervention received out of the protocol design will be excluded from the analysis (and listed separately).
Full Analysis Set (FAS)	[redacted]
Per-Protocol Analysis Set (PPAS)	[redacted]

	[redacted]

3.4 Statistical Analyses

Safety analyses will be performed on the SafAS3.

Immunogenicity analyses will be performed on PPAS3. If the difference between PPAS3 and FAS3 is greater than 10%, a supplemental analysis based on FAS3 will be performed to evaluate consistency of the results.

3.4.1 General Considerations

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

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

		Parameters
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 AE: Number and percentage (95% CIs) of participants. Unsolicited AE: Number and percentage (95% CIs) of participants and number of events.
Biological safety results	**Categorical data**	Number and percentage (95% CIs) of participants.
Immunogenicity	**Categorical data**	Number and percentage (95% CIs) of participants.

results	**(responders, fold-rise, titers ≥ cutoff)**	
	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).

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 normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) 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 means (GMs) and their 95% CI.

3.4.2 Primary Endpoints

3.4.2.1 Immunogenicity

The immunogenicity endpoints (RSV A and RSV B serum nAb titers) will be summarized by study intervention through the following parameters:

- GMT at D01 and D29, and 95% CI (as described in Section 3.4.1)
- GMT ratio (GMTR), i.e. post-vaccination titers at D29/pre-vaccination titers at D01, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)
- Percentages of participants with titers above predefined thresholds at D29, and 95% CI (using Clopper-Pearson method)
- Seroresponse rates, ie percentages of participants achieving several X-fold from pre- to post-vaccination at D29 (4-fold, 6-fold, 8-fold, 10-fold rise), and 95% CI (using Clopper-Pearson method)
- Reverse cumulative distribution curves (RCDCs) at D01 and D29

Pairwise comparisons between groups may be estimated:

- Ratio of GMT between 2 groups (RSV vs placebo), i.e. post-vaccination titers at D29 in RSV group/post-vaccination titers at D29 in placebo group, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)

- Difference of seroresponse rates between 2 groups (RSV vs placebo), i.e. seroresponse rate at D29 in RSV group – seroresponse rate at D29 in placebo group, and 95% CI (using Wilson Score method without continuity correction)

3.4.2.2 Safety

The safety endpoints after will be summarized by study group and described by frequencies and 95% CI using the exact binomial method (Clopper-Person method).

Safety analyses will include but are not limited to the following descriptions listed in Table 3.2:

Table 3.2: Statistical analyses for clinical safety objectives

Endpoint	Time	Description
Immediate unsolicited systemic AEs/ARs	Within 30 minutes after each vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest.
Solicited reactions: - solicited injection site reaction - solicited systemic reaction	Within 7 days after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest, and according to: - presence - time period - time of onset - maximum intensity - number of days of occurrence - action taken and discontinuation
Grade 3 Solicited reactions	Within 7 days after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest, and according to: - number of consecutive days of Grade 3 presence
Unsolicited AEs/ARs	Within 28 days after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of AEs/ARs, and according to: - maximum intensity - time of onset - duration - System Organic Class (SOC) and Preferred term (PT)
Grade 3 Unsolicited AEs/ARs	Within 28 days after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of AEs/ARs, and according to SOC and PT

MAAEs	Within 6 months after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of all and related MAAEs, and according to: - maximum intensity - System Organic Class (SOC) and Preferred term (PT)
AESIs	Within 6 months after vaccination	Summary Frequency Table presenting the number and percentage of participants experiencing the endpoint of interest as well as the number of all and related AESIs, and according to: - time of onset (D1-D4, D5-D8, D9-D15, D16-D29, D30-D45, D46-D60, D61-D75, D76-D90, D91-D120, D121-D180) - Outcome - System Organic Class (SOC) and Preferred term (PT)
SAEs	Within 6 months after vaccination	Summary Frequency Table presenting the number of participants experiencing the endpoint of interest as well as the number of SAEs. Summary Frequency Table will be presented according to: - time of onset (D1-D4, D5-D8, D9-D15, D16-D29, D30-D45, D46-D60, D61-D75, D76-D90, D91-D120, D121-D180) - seriousness criteria - outcome - and for all and related SAEs, by SOC and PT

In addition, biological safety will be analyzed by study intervention group, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) in general and according to severity grades. Biological safety will be analyzed at Screening visit, Visit 02 and Visit 03.

3.4.3 Secondary Endpoint

3.4.3.1 Immunogenicity

The immunogenicity endpoint (IgG Ab titers) will be summarized by study intervention through the following parameters:

- GMT at D01 and D29, and 95% CI (as described in Section 3.4.1)
- GMT ratio (GMTR), i.e. post-vaccination titers at D29/pre-vaccination titers at D01, and 95% CI (using normal approximation for the difference of log10 titers and then antilog)

- Percentages of participants with titers above predefined thresholds at D29, and 95% CI (using Clopper-Pearson method)
- Seroresponse rates, ie percentages of participants achieving several X-fold from pre- to post-vaccination at D29 (4-fold, 6-fold, 8-fold, 10-fold rise), and 95% CI (using Clopper-Pearson method)
- Reverse cumulative distribution curves (RCDCs) at D01 and D29

3.4.4 Other Safety Analyses

No other safety analyses will be planned.

3.4.5 Other Analysis

Other adhoc analyses could be performed depending on the needs of the study.

3.4.6 Handling of Missing Data and Outliers

3.4.6.1 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

3.4.6.1.1 Immediate

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

3.4.6.1.2 Causal Relationship

By convention, all events reported at the injection 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 CRF 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.
- If relationship to concomitant vaccine is collected, missing relationship to concomitant vaccine for unsolicited systemic AE will be considered as related to concomitant vaccine.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.6.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.6.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the section 4.2.1.2.3). 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.

3.4.6.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.6.2 Biological safety

No imputation of missing values and no search for outliers will be performed.

The main rule used is to not replace missing data at the time of the data capture.

For the computation of descriptive statistics, a value reported as:

- "< X" may be converted to a value of 0.5 *X,
- ">X" may be replaced by the X

In case of a high proportion of values below or above the detection limit, the clinical team might decide if such quantitative descriptive statistics should be produced.

If a subject has a missing baseline then the data for this subject will be included in the category "missing at baseline" in the table taking into account the baseline status. For grading scales defined with two conditions, one based on change from baseline and the second one based on the value at the visit, if the first condition is missing, the grading will be based only on the second condition.

3.4.6.3 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 4.2.4.1. In case of unplanned situation (e.g., large number of "haemolized serum" or "cold chain break" in BL identified by Global Clinical Immunology [GCI]), additional analyses could be proposed.

3.5 Sequence of Analyses

Multiple unblinded analyses will be performed:

- Safety analysis when safety data for 7 post-vaccination (D01-D08)
- Safety analysis when safety data for 28 post-vaccination (D01-D29)
- Immunogenicity analysis when immunogenicity data at D01 and D29

These analyses can be done jointly according to the availability of data.

A final analysis will be performed when all Stage 2 data have been collected.

3.6 Data Monitoring Committee (DMC)

A Cardiac Adjudication Committee (CAC), independent of the Sponsor, is planned to assess cardiac monitoring data (using standard case definition for standardized adjudication) in the event a participant develops symptoms suggestive of myocarditis, pericarditis, and/or myopericarditis.

4 Complementary Information on Assessment Methods

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

4.1 Complementary Information for Endpoint Assessment Method

Not applicable.

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 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).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as “No” and with all daily records missing (Unknown) then all daily intensities will be derived as None.

   Note: for data collected with eDiary, 1) is not applicable.

2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3. Note the intensity could be considered “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

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

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or 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 D1-D4, D5-D8, D9 and later.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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, D1-D4, D5-D8.

4.2.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.2.1.1.6 Overall Number of Days of Occurrence

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), the overall number of days of presence will be considered as Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 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.

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

4.2.1.2 Unsolicited AEs

4.2.1.2.1 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.

4.2.1.2.2 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 of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

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

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

4.2.1.2.3 Last Vaccination

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

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.2.1.2.4 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 4.2.1.2.3:

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

The time of onset is considered 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, which corresponds to AEs with a time of onset between 1 and 29 days or missing / between injection and the next visit or missing (upper limit of the time window of the next visit if visit not done)>. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the section 4.2.1.2.3), so will be included in these tables.

Time of onset period is displayed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

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

4.2.1.2.5 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.

4.2.1.2.6 Medically-Attended Adverse Event

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

MAAE will be analyzed during the following time periods:

- Within 28 days
- During the 6-month follow-up period (i.e., from 29 days after the injection)
- During the study (i.e., all MAAEs occurred during the study)

4.2.1.2.7 Serious Adverse Events

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

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

- Within 28 days
- During the 6-month follow-up period (i.e., from 29 days after the injection)
- During the study (i.e., all SAEs occurred during the study)

4.2.1.2.8 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 CRF.

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

- Within 28 days
- During the 6-month follow-up period (i.e., from 29 days after the injection)
- During the study (i.e., all AESIs occurred during the study)

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.3 Seriousness

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

4.2.2.4 Outcome

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

4.2.2.5 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 3.4.6.1.2. Relationship to study procedure is only presented in the listing.

4.2.2.6 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, 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.

4.2.3 Biological Safety

4.2.3.1 Standardized Unit

The standardization of laboratory units will be performed using the International System Units. If different units appear in the same trial (e.g., if more than one laboratory is involved), then measurements should be appropriately standardized to allow a unified evaluation.

4.2.3.2 Normalization

Initial laboratory data are transformed into normalized results in the study data tabulation model (SDTM), via clinical data management tool.

4.2.3.3 Intensity

Intensity for biological parameters will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing. If the FDA toxicity grading scale is used, Grade 3 covers both Grade 3 and 4 abnormalities as defined in the guideline.

The measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol/SAP;

The maximum intensity corresponds to the highest intensity for a unique parameter over the period considered.

In addition, intensity thresholds for some laboratory abnormalities will be derived, as detailed in Table 4.1 (which is adjusted from Table 34 of the protocol to avoid gaps in the thresholds between two grades). The derivation is based on normalized results.

Table 4.1: Precisions for the derivation of the intensity thresholds for laboratory abnormalities

Laboratory Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Female) Absolute value – gm/dL	10.9 < value ≤ 12.0	9.4 < value ≤ 10.9	≤ 9.4
Hemoglobin (Female) change from baseline value (post value - baseline value) – gm/dL	-1.5 ≤ value < 0	- 2.0 ≤ value < -1.5	< -2.0
Hemoglobin (Male) Absolute value – gm/dL	12.4 < value ≤ 13.5	10.4 < value ≤ 12.4	≤ 10.4
Hemoglobin (Male) change from baseline value (post value - baseline value) – gm/dL	-1.5 ≤ value < 0	- 2.0 ≤ value < -1.5	< -2.0
Increase in WBC – cell/mm^3	10 800 ≤ value ≤ 15 000	15 000 < value ≤ 20 000	> 20 000
Decrease in WBC – cell/mm^3	2500 ≤ value ≤ 3500	1500 ≤ value < 2500	< 1500
Decrease in absolute Lymphocytes – cell/mm^3	750 ≤ value ≤ 1000	500 ≤ value < 750	< 500
Decrease in absolute Neutrophils – cell/mm^3	1500 ≤ value ≤ 2000	1000 ≤ value < 1500	< 1000
Eosinophils – cell/mm^3	650 ≤ value ≤ 1500	1500 < value ≤ 5000	> 5000
Decrease in Platelets – cell/mm^3	125 000 ≤ value ≤ 140 000	100 000 ≤ value < 125 000	< 100 000
PT – increase by factor (prothrombin time)	1.00 x ULN ≤ value < 1.11 x ULN	1.11 x ULN ≤ value ≤ 1.20 x ULN	>1.20 x ULN

Laboratory Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
PTT – increase by factor (partial thromboplastin time)	1.00 x ULN ≤ value <1.21 x ULN	1.21 x ULN ≤ value ≤ 1.40 x ULN	> 1.40 x ULN
Creatinine – mg/dL	1.5 ≤ value ≤ 1.7	1.7 < value ≤ 2.0	> 2.0
Alkaline phosphate – increase by factor	1.1 x ULN ≤ value < 2.1 x ULN	2.1 x ULN ≤ value ≤ 3.0 x ULN	> 3.0 x ULN
ALT (increase by factor)	1.1 x ULN ≤ value < 2.6 x ULN	2.6 x ULN ≤ value ≤ 5.0 x ULN	> 5.0 x ULN
AST (increase by factor)	1.1 x ULN ≤ value < 2.6 x ULN	2.6 x ULN ≤ value ≤ 5.0 x ULN	> 5.0 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test; increase by factor	1.1 x ULN ≤ value < 1.26 x ULN	1.26 x ULN ≤ value ≤ 1.5 x ULN	> 1.5 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 x ULN ≤ value < 1.6 x ULN	1.6 x ULN ≤ value ≤ 2.0 x ULN	> 2.0 x ULN

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal; WBC, white blood cell, LLN, lower limit of normal

4.2.4 Immunogenicity

4.2.4.1 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 (BL) 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

4.2.4.2 Seroprotection

Not applicable.

4.2.4.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes the denominator.

- If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is 1
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is (LLOQ/2) / baseline computed value
- If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value /LLOQ

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

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.2.4.4 Seroconversion

Not applicable.

4.2.5 Derived Other Variables

4.2.5.1 Age for Demographics (in years)

Considering the Sponsor convention of Date Of Birth (DOB) collection, the age of a study participant at the date of visit 1(V01) will be entered or computed automatically in the electronical CRF and presented as an integer.

4.2.5.2 Duration of a study participant participation

The duration of a study participant participation in the study is computed as follows:

Maximum (Termination date, Follow-up date) - V01 date + 1.

4.2.5.3 Duration of the Study

The durations are computed in days as follows: Latest period date - Earliest period date + 1.

5 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
DMC	Data Monitoring Committee
FAS	Full analysis set
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	Geometric mean
GMT	Geometric mean of titer
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NC	Not computed
NIMP	Non- Investigational Medicinal Product
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
SOC	(Primary) System organ class
PT	Preferred term
TLF	Tables, listings and figures
ULOQ	Upper level of quantitation

7 References

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