Clinical Study Protocol

Protocol 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

Amendment Number: 2

Compound: RSV pre-F mRNA in an LNP, 4 doses: [redacted] µg, [redacted] µg, [redacted] µg, or [redacted] µg

Brief Title: Study of a Respiratory Syncytial Virus mRNA candidate encapsulated in a lipid nanoparticle-based formulation in adults aged 18 to 50 years and 60 years and older

Study Phases: Phase I/IIa

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer: Sanofi Pasteur S.A., Campus Mérieux, 1541 avenue Marcel Mérieux, 69280 Marcy L'Étoile, France

Regulatory Agency Identifier Number(s):

BB-IND: 007168
WHO UTN: U1111-1271-1514
BGTD File: TBD

Protocol Version Number: 7.0

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Medical Monitor(s) Name and Function:
Responsible medical officer (RMO): [redacted] **(Stage 1)**
[redacted] **(Stage 2)**

The study centers and the investigators at each center are listed in a separate document.

Document History and Protocol Amendment Rationale

Previous Version(s)	Date	Comments
1.0	15-Apr-2022	Version not submitted
2.0	13-May-2022	Version not submitted
3.0	21-Jun-2022	Version not submitted
4.0	23-Jun-2022	Version not used in the study
5.0	22-Sep-2022	Original version used in the study
6.0	27-Jul-2023	Amendment 1

Overall Rationale for the Amendment:

The main reason for updating protocol version 6.0 to protocol version 7.0 (Amendment 2) is to revise the study 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 study Stage 1.

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Abbreviations

Ab	antibody
AE	adverse events
AESI	adverse events of special interest
AIT	Additional Immunogenicity Testing subset
ALT	alanine aminotransferase
AR	adverse reactions
ARD	acute respiratory disease
AST	aspartate aminotransferase
BL	blood sample for immunogenicity
BS	blood sample for safety
BUN	blood urea nitrogen
CAC	Cardiac Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CMI	cell-mediated immunity
COVID-19	coronavirus disease 2019
CRF	case report form
D	Day
DC	diary card
DNA	deoxyribonucleic acid
DOPE	1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine
CRF	case report form (electronic)
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ESDR	early safety data review
EU	European Union
FAS	Full Analysis Set
FD3	membrane-bound pre-fusion F
GCP	Good Clinical Practice
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
HIV	human immunodeficiency virus
HRP	horseradish peroxidase
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IgG	immunoglobulin G
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IRT	interactive response technology
IU	international unit
LLN	lower limit of normal
LLT	lowest level term
LNP	lipid nanoparticle
LRTD	lower respiratory tract disease
MA	memory aid
MAAE	medically attended adverse event
MAARD	medically attended acute respiratory disease
MCD	Minimal Change Disease
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
mRNA	messenger ribonucleic acid
N/A	not applicable
nAb	neutralizing antibody
NHP	non-human primate
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
PBS	phosphate buffered saline
PEG	polyethylene glycol
PPAS	Per-Protocol Analysis Set
pre-F	pre-fusion F
PRNT	Plaque Reduction Neutralization Test
PSB	Product Safety Board
PT	prothrombin time
PTT	partial thromboplastin time
PV	pharmacovigilance
RAC	Respiratory Adjudication Committee
RBC	red blood cell
RCDC	reverse cumulative distribution curve
RMO	Responsible Medical Officer

RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious AE
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SERT	Safety Evaluation Review Team
SD	standard deviation
SMT	safety management team
SoA	Schedule of Activities
TBD	to be determined
ULN	upper limit of normal
US	United States
UTN	universal trial number
Vac	vaccination
WB	blood sample for Cell-mediated Immunity subset
WBC	white blood cell
WHO	World Health Organization

1 Protocol Summary

1.1 Synopsis

Study VAE00010 includes 2 stages: Phase I/IIa (Stage 1) and Phase IIa dose-ranging stage (Stage 2). These 2 stages are described separately throughout the document, as necessary, for clarity.

Protocol 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

Brief Title:

Study of a Respiratory Syncytial Virus mRNA candidate encapsulated in a lipid nanoparticle-based formulation in adults aged 18 to 50 years and 60 years and older

Regulatory Agency Identifier Number(s):

BB-IND: 007168

WHO UTN: U1111-1271-1514

BGTD File: TBD

1.1.1 Stage 1 (Phase I/IIa)

Rationale:

The aim of the Phase I/IIa stage of this study is to evaluate the safety and immunogenicity of 3 different doses (ie, low dose [[redacted] µg], medium dose [[redacted] µg], and high dose [[redacted] µg]) of respiratory syncytial virus (RSV) messenger ribonucleic acid (mRNA) vaccine candidate encapsulated in either of 2 different lipid nanoparticle (LNP)-based formulations (ie, LNP containing [redacted] or LNP containing [redacted]).

Phase I/IIa is designed to address the following goals:

- Assess the safety profile of the candidate formulations
- Describe the immunogenicity profile of the candidate formulations
- Select the LNP
- Evaluate different dose ranges (low, medium, or high) to inform subsequent clinical studies
- Assess the safety and immunogenicity of a booster vaccination of the selected formulation administered 12 months after the primary vaccination in a subset of the study population

Objectives and Endpoints

Objectives	Endpoints
Primary	
Safety Objective To assess the safety profile 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]	***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 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 containing either of 2 different LNPs	***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

Overall Design of Stage 1

Type of design	Sequential (Phase I)/ parallel (Phase IIa), multi-center
Phase	I/IIa
Control method	Placebo-controlled
Study population	Healthy adults aged 18 to 50 years, and 60 years and older
Countries	US, Puerto Rico, Australia*
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 and Booster Cohorts: 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
Investigational intervention assignment method	Randomization

* It is to be noted that the list of participating countries may be modified based on the study evolution.

Inclusion/Exclusion Criteria for Stage 1

Inclusion Criteria

Inclusion Criteria to be Checked at Screening

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Sentinel Cohort: Aged 18 to 50 years on the day of inclusion

Main Cohort: Aged 60 years or older on the day of inclusion[a]

Sex, contraceptive/barrier method and pregnancy testing requirements

I02: Sentinel Cohort: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration

Main and Booster Cohorts: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Informed consent

I04: Informed consent form has been signed and dated

Inclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are eligible for the study only if all of the following criteria are met:

Age

I01:Sentinel Cohort: Aged 18 to 50 years on the day of inclusion

Main Cohort: Aged 60 years or older on the day of inclusion[a]

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Sex, contraceptive/barrier method and pregnancy testing requirements

I05: Sentinel Cohort: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

OR

[a] "60 years of age or older" means from the day of the 60th birthday.

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) before the first dose of study intervention.

Main and Booster Cohorts: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

Exclusion criteria

Exclusion Criteria to be Checked at Screening

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[a]; any allergic reaction (eg, anaphylaxis) after administration of a mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[b] in the 3 weeks preceding inclusion, contraindicating IM injection

[a] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[b] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[a]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[b]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[b]

E11: Previous vaccination against RSV with an investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

E13: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E16: Self-reported or documented human immunodeficiency virus (HIV) detected by any FDA-approved / validated test, hepatitis B virus surface antigen (HBsAg), hepatitis B core antibodies (HBcAb), hepatitis C virus antibodies (HCV Abs), or positive SARS-CoV-2 RT-PCR or antigen test[c]

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[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[b] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

[c] Participants must not have had a positive SARS-CoV-2 RT-PCR or antigen test or self-reported COVID-19 in the 10 days prior to the visit; a prospective participant should not be included in the study until the condition has resolved. A diagnostic test for SARS-CoV-2 is not mandatory for screening. Investigators may perform screening SARS-CoV-2 testing at their discretion

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

Exclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[a]; any allergic reaction (eg, anaphylaxis) after administration of a mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[b] in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

[a] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[b] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[a]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[a]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

E13: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

E18: Participants with a Screening electrocardiogram that is consistent with possible myocarditis, pericarditis, and/or myopericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E19: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E20: Any screening laboratory parameter with laboratory abnormalities that are greater than Grade 1 or deemed clinically significant in the opinion of the investigator

[a] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

Brief Summary of Stage 1:

The purpose of Stage 1 (Phase I/IIa) is to assess the safety and immunogenicity of a single intramuscular (IM) injection of 3 dose-levels of an RSV mRNA vaccine candidate formulated with 2 different LNPs (ie, LNP containing [redacted] or [redacted]) in healthy adult participants aged between 18 to 50 years, and 60 years and older. The primary objectives of this stage are to assess the safety and immunogenicity profiles across the dose-level groups (low, medium, and high doses) with 2 LNPs ([redacted] and [redacted]). This stage will evaluate the safety and immunogenicity of a booster vaccination administered 12 months after the primary vaccination in a subset of the study population.

Study details include:

Study Duration:

12 months for the Sentinel and Main Cohorts, 24 months overall for the subset of participants enrolled in the Booster Cohort.

Treatment Duration:

Sentinel Cohort:1 IM injection. Participants will be followed for 12 months post-vaccination.

Main Cohort: 1 IM injection. Participants will be followed for 12 months post-vaccination.

Booster Cohort: 1 IM injection 12 months after the primary vaccination (Main Cohort). Participants will be followed for 12 months after administration of the booster dose.

Visit Frequency:

Sentinel Cohort: A screening visit and 7 planned site visits are scheduled to occur at Day (D) -14 to -01, D01, D04, D08, D29, 3 months, 6 months, and 12 months.

Main Cohort: A screening visit and 6 planned site visits are scheduled to occur at -D14, D01, D08, D29, 3 months, 6 months, and 12 months.

Booster Cohort: The subset of participants from the Main Cohort who are enrolled in the Booster Cohort will attend a total of 12 planned site visits:

- A screening visit and 6 planned site visits during the Main Cohort
- A screening visit before enrollment in the Booster Cohort and 6 planned site visits. 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). Participants will receive a booster vaccination 12 months post-primary vaccination at Visit 08. Following the booster vaccination, participants will return to the site at D08, D29, 3 months, 6 months, and 12 months.

Participants who report a respiratory infection or an SAE may be requested to attend a Respiratory Illness Visit (either at home or on site, depending on circumstances) for the collection of a nasal swab specimen for the detection of RSV and respiratory pathogens (including COVID-19).

Number of Participants:

A total of 790 participants are planned to be randomized, with 90 participants in the Sentinel Cohort and 700 participants in the Main Cohort (see tables below). Approximately 200 participants from the Main Cohort will be enrolled in the Booster Cohort (see table below). It

is also planned for 140 participants (ie, 20 participants per arm) 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.

For the Main Cohort, it is also planned to enroll approximately [redacted] (ie, minimum of approximately 42 participants / [redacted]).

Planned sample size for the Sentinel Cohort Phase I/IIa (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

LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; N/A: not applicable; RSV: respiratory syncytial virus; SC: Sentinel Cohort

Planned sample size for the Main Cohort Phase I/IIa (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

LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; N/A: not applicable; RSV: respiratory syncytial virus

Planned sample size for the Booster Cohort Phase I/IIa (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 without considering the drop-out rate at the time of booster vaccination. Participants in the Booster Cohort will be randomized to receive either a booster dose of the selected formulation or placebo.

[a] Includes participants either 1) born in Japan with Japanese biological parents and currently living in a foreign country, or 2) second-generation Japanese: born in a foreign country with Japanese biological parents who were born in Japan and moved to a foreign country (based on Japan's Pharmaceuticals and Medical Devices Agency recommendations). The proportion of participants of Japanese origin included in the study may be modified.

Intervention Groups and Duration:

In the Sentinel Cohort, enrollment of participants and dose-escalation was performed in a stepwise manner. Starting with the low dose formulations, and for each of the 3 dose-levels, eligible participants were randomized in a 1:1:1 ratio to receive a single administration of RSV mRNA vaccine with an LNP containing [redacted], RSV mRNA vaccine with an LNP containing [redacted], or placebo.

Enrollment was paused before each dose-escalation for each of the 3 dose-levels in the Sentinel Cohort, the goal of which was to allow for a cautious, stepwise approach to vaccine dose-escalation. An internal SMT performed the ESDRs. Safety reviews completed in each ESDR by the SMT included an assessment of the following safety parameters: immediate unsolicited AEs, solicited injection site and systemic reactions, biological safety laboratory abnormalities, unsolicited AEs reported as related by the investigator, MAAEs, AESIs, and SAEs. The initiation of enrollment for the subsequent dose-levels of the Sentinel Cohort was dependent on a favorable SMT review. Enrollment of the Sentinel Cohort and planned safety assessments were completed.

Full enrollment of the Main Cohort proceeded as no safety issues were identified during the ESDRs. Eligible participants were randomized in a 1:1:1:1:1:1:1 ratio for the Main Cohort to receive a single IM administration of 1 of 3 different dose-levels of RSV mRNA vaccine with an LNP containing [redacted], RSV mRNA vaccine with an LNP containing [redacted], or placebo.

At the time of this Amendment, enrollment and planned safety assessments for the Main Cohort have been completed, with no safety issues identified. Safety data showed that all RSV mRNA formulations were generally well tolerated. Between the tested LNPs, [redacted] showed a trend of better reactogenicity compared with [redacted], in particular with injection site pain and myalgia, which were the most frequently reported solicited reactions. These reactions were generally mild to moderate in severity, with few Grade 3 reactions. Unsolicited AEs reported up to 28 days after vaccination were overall balanced across mRNA groups, and no dose response was observed. Increases from baseline in Troponin I levels seen at D08 in 5 participants in the mRNA intervention groups were considered not clinically meaningful. There were no AESIs, no deaths and few SAEs reported up to 28 days after vaccination. Two SAEs within 28 days post-vaccination were assessed as related to the study vaccine by investigator (Minimal Change Disease [MCD] and myocardial injury). Both related SAEs had possible alternative etiologies:

- A 68-year-old male participant with no ongoing medical history was diagnosed with Minimal Change Disease 9 days after the administration of the study intervention. The participant had no concomitant medications except non-steroidal anti-inflammatory drugs (ibuprofen) taken 8 days before onset of the event. Considering insufficient evidence to support a causal association with the study vaccine and NSAIDs known as potential cause of kidney problems (including MCD), Sanofi assessed this event as not related to the study vaccine.
- A 61-year-old male participant was diagnosed as with asymptomatic myocardial injury (adjudicated by Cardiac Adjudication Committee as “Other Cardiac Vascular events, Acute myocardial injury”) characterized by an asymptomatic and isolated rise in high sensitivity troponin 8 days after administration of the study intervention. This participant had no cardiac history or known risk factors for myocarditis (apart from sex and age). However, he had a long hike the day before troponin I testing for which strenuous exercise

is known as a potential cause of troponin increase, and his family history included father with coronary artery bypass graft and mother with stents and pacemaker. The participant remained asymptomatic, stable, with fairly rapid fall of troponin value and no other AEs were reported. He recovered without sequalae. Considering time to onset, uncertainties on causes of this isolated troponin increase, and limited current knowledge on this RSV mRNA vaccine, Sanofi conservatively assesses this event as related to the study vaccine even if there are suspicions of underlying conditions leading to this asymptomatic myocardial injury.

Immunogenicity results will be described in the Stage 2 section of this protocol.

Eligible participants will be screened and enrolled in the Booster Cohort to receive a booster vaccination 12 months after the primary vaccination. Approximately 200 participants from the Main Cohort (100 participants from the selected formulation group and 100 participants from the placebo group) will be randomized at Visit 08 in a 1:1 ratio to receive a booster vaccination of the selected formulation of RSV mRNA vaccine or placebo. The dose-level and the LNP formulation will be selected based upon the Main Cohort safety and immunogenicity results.

The duration of participation will be approximately 12 months for participants in the Sentinel and Main Cohorts. The subset of participants from the Main Cohort that will be enrolled in the Booster Cohort will be in the study for an additional 12 months (ie, approximately 24 months total duration).

Study Interventions

Form: Liquid frozen solution in a vial

Composition: One dose ([redacted] mL) contains:

[redacted]

- Diluent: [redacted]x PBS

Route of administration: IM

Statistical Considerations:

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

Primary and secondary safety endpoints

Safety endpoints will be described for each study intervention and according to the study intervention received. The main parameters will be described using 95% confidence interval (CI).

Primary and secondary immunogenicity endpoints

Immunogenicity endpoints will be described using 95% CI for each study intervention group according to the group of randomization.

Independent Data Monitoring Committee: No

This stage does not utilize an independent data monitoring committee, however, internal committees are utilized to monitor participant safety. These include an unblinded Sponsor Safety Management Team (SMT) (unblinded for only the Sentinel Cohort), a Product Safety Board (PSB), and an internal Sponsor Safety Evaluation Review Team (SERT).

In addition, a Cardiac Adjudication Committee (CAC), independent of the Sponsor, is planned for monitoring cardiac data in the event a participant develops symptoms of myocarditis, pericarditis, and/or myopericarditis.

1.1.2 Stage 2 (Phase IIa dose-ranging)

Rationale:

RSV is the leading viral agent causing severe respiratory tract disease worldwide in older adults. There is a medical need to improve patient quality of life by preventing lower respiratory tract disease (LRTD).

Study VAE00010 also includes a Stage 2 (Phase IIa dose-ranging stage) that will enroll approximately 75 adults aged 60 years and older to assess the safety and immunogenicity of the LNP selected in Stage 1 (Phase I/IIa), with [redacted] µg and [redacted] µg doses of RSV mRNA vaccine. During Stage 1, the [redacted] µg dose of RSV mRNA vaccine combined with the selected LNP showed the highest immune response with a favorable safety profile; it is expected that the [redacted] µg dose of RSV mRNA vaccine with the selected LNP will show a better immune response.

Phase IIa dose-ranging stage of this study is designed to:

- Assess the safety of the RSV mRNA vaccine [redacted] µg and [redacted] µg doses with the selected LNP ([redacted])
- Describe the immunogenicity profile of the RSV mRNA vaccine [redacted] µg and [redacted] µg doses with the selected LNP ([redacted])

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

Objectives	Endpoints
	• 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 To assess the immunogenicity of 2 different dose-levels of RSV mRNA vaccine containing [redacted]	***Immunogenicity Endpoint*** RSV A and RSV B serum nAb titers at pre-vaccination (D01) and 28 days post-vaccination (D29)
Secondary	
Immunogenicity Objective To assess the immune response at 28 days following vaccination on D01	***Immunogenicity Endpoint*** Serum anti-F immunoglobulin G (IgG) Ab titers at pre-vaccination (D01) and 28 days (D29) post-vaccination

Overall Design of Stage 2

Type of design	Phase IIa parallel, multi-center, dose-ranging
Phase	IIa
Control method	Placebo-controlled
Study population	Adults aged 60 years and older
Countries	US*
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

* It is to be noted that the list of participating countries may be modified based on the study evolution.

Inclusion/Exclusion Criteria for Stage 2 – Phase IIa dose-ranging

Inclusion Criteria

Inclusion Criteria to be Checked at Screening and at Visit 01 (Day 01)

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Aged 60 years or older on the day of inclusion[a]

Sex, contraceptive/barrier method and pregnancy testing requirements

I02: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Informed consent

I04: Informed consent form has been signed and dated

Exclusion criteria

Exclusion Criteria to be Checked at Screening

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[b]; any allergic reaction (eg, anaphylaxis) after administration of a mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

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[a] "60 years of age or older" means from the day of the 60th birthday.

[b] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[a] in the 3 weeks preceding inclusion, contraindicating IM injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[b]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[c]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[c]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E16: Self-reported or documented human immunodeficiency virus (HIV) detected by any FDA-approved / validated test, hepatitis B virus surface antigen (HBsAg), hepatitis B core

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[a] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[c] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

antibodies (HBcAb), hepatitis C virus antibodies (HCV Abs), or positive SARS-CoV-2 RT-PCR or antigen test[a]

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

Exclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[b]; any allergic reaction (eg, anaphylaxis) after administration of a mRNA vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[c] in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[d]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

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[a] Participants must not have had a positive SARS-CoV-2 RT-PCR or antigen test or self-reported COVID-19 in the 10 days prior to the visit; a prospective participant should not be included in the study until the condition has resolved. A diagnostic test for SARS-CoV-2 is not mandatory for screening. Investigators may perform screening SARS-CoV-2 testing at their discretion.

[b] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[c] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[d] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[a]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[a]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

E18: Participants with a Screening electrocardiogram that is consistent with possible myocarditis, pericarditis, and/or myopericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E19: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E20: Any screening laboratory parameter with laboratory abnormalities that are greater than Grade 1 or deemed clinically significant in the opinion of the investigator

E21: Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study before the end of the study or planning participation in strenuous or endurance exercise through V03.

[a] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information

If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

Brief Summary of Stage 2:

Study VAE00010 also incorporates a Stage 2 (Phase IIa, dose-ranging design) that includes adults aged 60 years and older to assess the safety and immunogenicity of [redacted] µg and [redacted] µg doses of RSV mRNA vaccine encapsulated in LNP [redacted]. In the Phase IIa dose-ranging stage, 75 eligible participants will be randomly assigned in a 1:1:1 ratio to receive a single IM administration of RSV mRNA vaccine candidate [redacted] µg or [redacted] µg, or placebo. Multiple safety analyses will be performed, minimally at D07 and D28. Additional analyses may be performed as data are available.

Phase IIa dose-ranging stage will be conducted in the US[a].

Study details include:

Study Duration:

Approximately 6 months for participants

Treatment Duration:

1 IM injection. Participants will be followed for approximately 6 months post-vaccination

Visit Frequency:

A screening visit and 4 planned site visits are scheduled to occur at Day (D) -14 to -01, D01, D04, D08, and D29

Number of Participants:

In Phase IIa dose-ranging stage, a total of 75 participants are planned to be randomized (25 participants per arm):

Planned sample size for Phase IIa dose-ranging (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

Study Arms and Duration:

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.

The duration of participation will be approximately 6 months for participants.

[a] It is to be noted that the list of participating countries may be modified based on the study evolution.

Study Interventions

Form: Liquid frozen solution in a vial

Composition: One dose ([redacted] mL) contains:

- [redacted] µg or [redacted] µg of RSV pre-F mRNA
- LNP containing [redacted]
- Diluent: PBS [redacted]x
- Route of administration: IM injection

Placebo

- Form: Liquid solution in a vial
- Composition: [redacted]% normal saline
- Route of administration: IM injection

Statistical considerations:

Primary safety endpoints

Safety endpoints will be described for each study intervention and according to the study intervention received. The main parameters will be described using 95% CIs.

Primary immunogenicity endpoint

Immunogenicity endpoint will be described using 95% CIs for each study intervention group according to the group of randomization.

Independent Data Monitoring and Independent Adjudication Committees: Yes

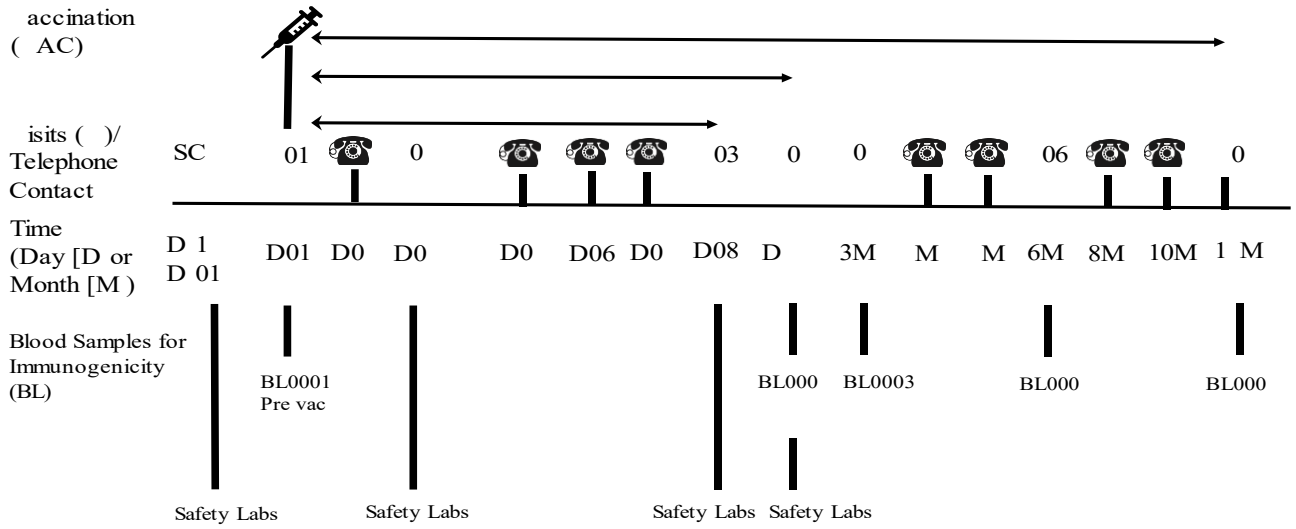
A Cardiac Adjudication Committee (CAC), independent of the Sponsor, is planned to assess cardiac monitoring data (using standard case definition for standardized adjudication) in the event a participant develops symptoms suggestive of myocarditis, pericarditis, and/or myopericarditis.

1.2 Schema

1.2.1 Stage 1 (Phase I/IIa)

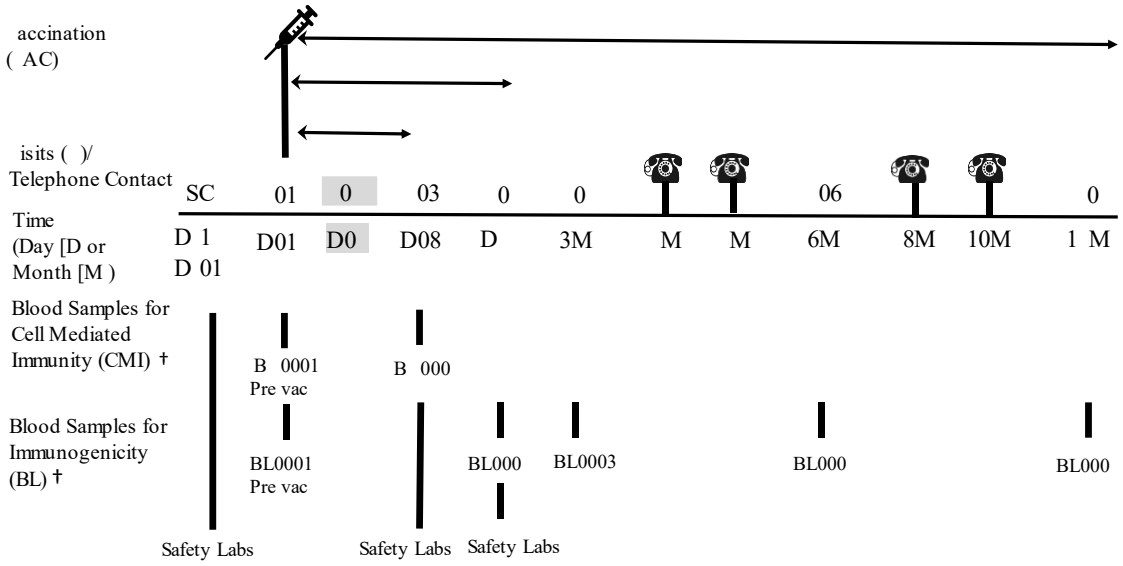
The graphical designs of Study VAE00010 Phase I/IIa are presented in Figure 1, Figure 2, and Figure 3. The schematic representation of the enrollment strategy is presented in Figure 4.

Figure 1: Graphical study design (Stage 1) - Sentinel Cohort Phase I/IIa (participants aged 18 to 50 years)



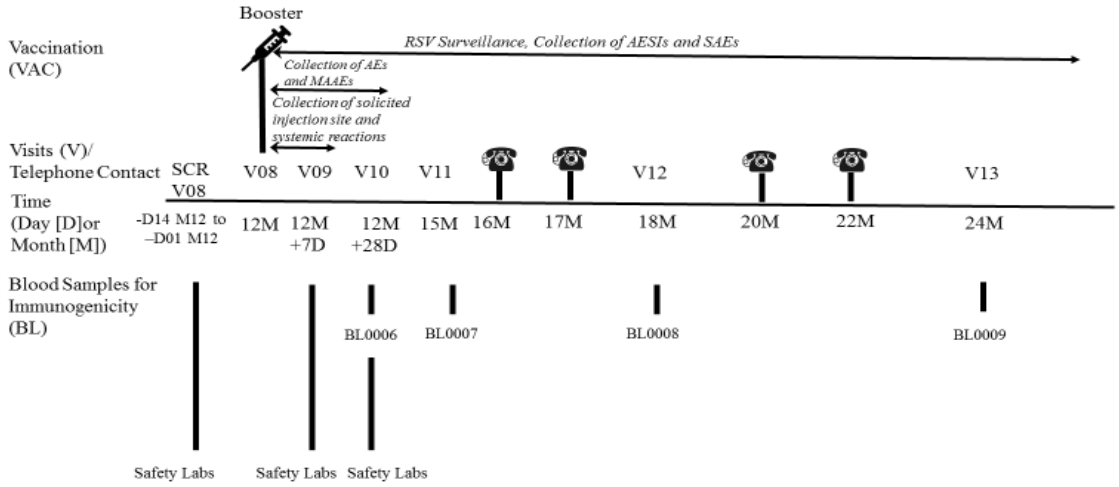
AE: adverse event; AESI: adverse event of special interest; BL: blood sample; MAAE: medically attended adverse event; RSV: respiratory syncytial virus; SAE: serious adverse event; SCR: Screening
Note: D01 (V01) blood sampling to be completed prior to vaccination.

Figure 2: Graphical study design (Stage 1) - Main Cohort Phase I/IIa (participants aged 60 years and older)



AE: adverse event; AESI: adverse event of special interest; BL: blood samples for immunogenicity; MAAE: medically attended adverse event; RSV: respiratory syncytial virus; SAE: serious adverse event; SCR: Screening; VAC: vaccine; WB: blood sample for CMI
* D04 (V02) does not apply to the Main Cohort
† D01 (V01) blood sampling to be completed prior to vaccination.

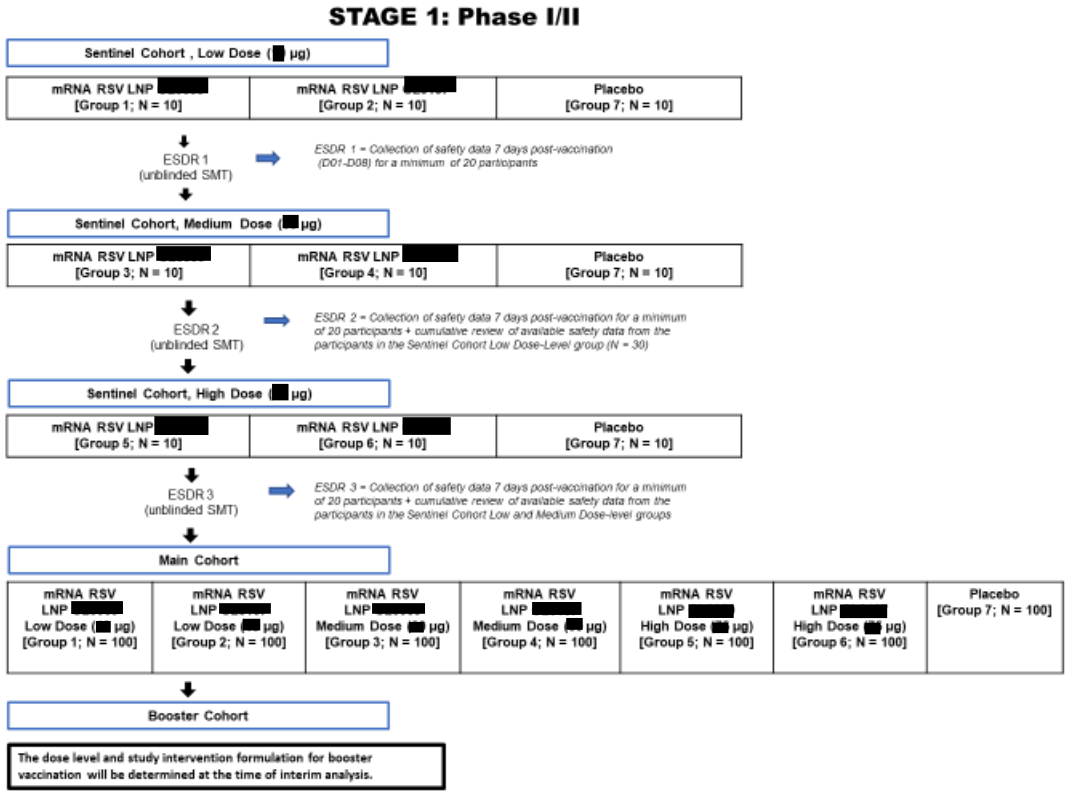
Figure 3: Graphical study design (Stage 1) - Booster Cohort Phase I/IIa (participants aged 60 years and older)



AE: adverse event; AESI: adverse event of special interest; BL: blood samples for immunogenicity; MAAE: medically attended adverse event; RSV: respiratory syncytial virus; SAE: serious adverse event; SCR: Screening

Note 1: Approximately 200 participants, 100 participants from the selected formulation group and 100 participants from the placebo group, will be randomized at M12 in a 1:1 ratio to receive a booster vaccination of the selected formulation of RSV mRNA vaccine (ie, the dose-level and the LNP formulation selected based upon the Main Cohort safety and immunogenicity results) or placebo.
Note 2: BL0005, obtained at V07 of Main Cohort, will be used as the pre-vaccination sample in the Booster Cohort.

Figure 4: Enrollment strategy - Stage 1 (Phase I/IIa)

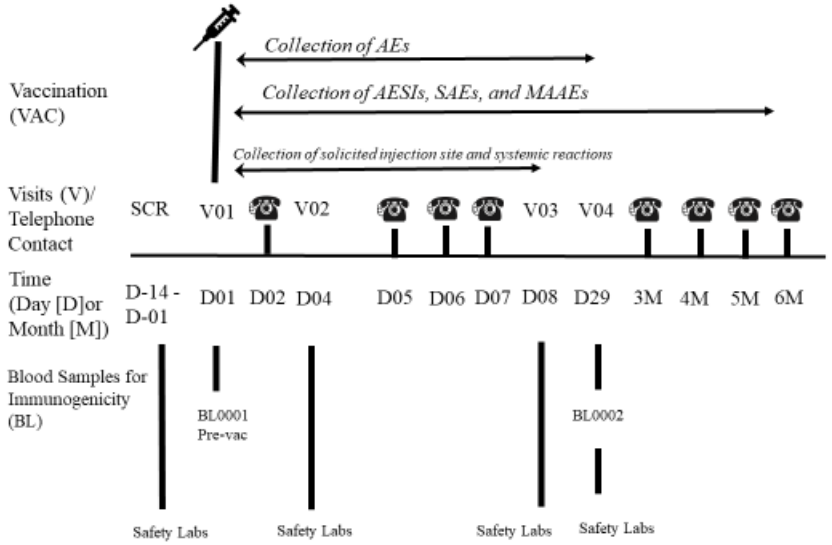


ESDR: early safety data review; LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; RSV: respiratory syncytial virus; SMT: safety management team

1.2.2 Stage 2 (Phase IIa dose-ranging)

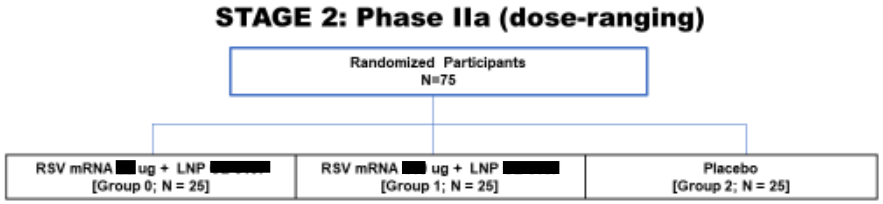
The graphical design of Study VAE00010 Phase IIa dose-ranging stage is presented in Figure 5. The schematic representation of the enrollment strategy is presented in Figure 6.

Figure 5: Graphical study design - Stage 2 (Phase IIa dose-ranging)



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.

Figure 6: Enrollment strategy - Stage 2 (Phase IIa dose-ranging)



LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid.

1.3 Schedule of Activities (SoA)

1.3.1 Stage 1 (Phase I/IIa)

Table 1: 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†	

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**	
Electrocardiogram‡	*X*	X												
Pre-vaccination temperature§			X											
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	

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 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***		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). 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 2: 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). 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 3: 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

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 solicited injection site and systemic reactions‡‡‡	*X*		7 days after vaccination								
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.

†† BL000 , obtained at 0 , 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). 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.

1.3.2 Stage 2 (Phase IIa dose-ranging)

Table 4: Schedule of activities Phase IIa dose-ranging stage (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								

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**		
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		
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							

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 MAAEs‡‡	*X*		Throughout the study							
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; SAE: serious adverse event; TC: telephone call; 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). 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.

2 Introduction

Sanofi's respiratory syncytial virus (S) m NA vaccine candidate is a novel vaccine that is being developed for preventing lower respiratory tract disease (LRTD) caused by RSV in older adults (60 years of age and older).

2.1 Study Rationale

2.1.1 Stage 1 (Phase I/IIa)

The aim of the Phase I/IIa stage of this study is to evaluate the safety and immunogenicity of 3 different doses (ie, low dose [[redacted] µg], medium dose [[redacted] µg], or high dose [[redacted] µg]) of an RSV mRNA vaccine candidate encapsulated in 2 different lipid nanoparticle (LNP)-based formulations (ie, an LNP containing either [redacted] or [redacted]) in 790 participants aged 18 to 50 years, and 60 years and older.

Phase I/IIa of this study is designed to address the following goals:

- Assess the safety profile of the candidate formulations
- Describe the immunogenicity profile of the candidate formulations
- Select the LNP
- Evaluate different dose ranges (low, medium, or high) to inform subsequent clinical studies
- Assess the safety and immunogenicity of a booster vaccination administered 12 months after the primary vaccination in a subset of the study population

2.1.2 Stage 2 (Phase IIa dose-ranging)

RSV is the leading viral agent causing severe respiratory tract disease worldwide in older adults. There is a medical need to improve patient quality of life by preventing LRTD.

Study VAE00010 also includes a Stage 2 (Phase IIa dose-ranging stage) that will enroll approximately 75 adults aged 60 years and older to assess the safety and immunogenicity of the LNP selected in Stage 1 (Phase I/IIa), with [redacted] µg and [redacted] µg doses of RSV mRNA vaccine. During Stage 1, the [redacted] µg dose of RSV mRNA vaccine combined with the selected LNP showed the highest immune response with a favorable safety profile; it is expected that the [redacted] µg dose of RSV mRNA vaccine with the selected LNP will show a better immune response.

Phase IIa dose-ranging stage of this study is designed to:

- Assess the safety of the RSV mRNA vaccine [redacted] µg and [redacted] µg doses with the selected LNP ([redacted])
- Describe the immunogenicity profile of the RSV mRNA vaccine [redacted] µg and [redacted] µg doses with the selected LNP ([redacted])

2.2 Background

Respiratory Syncytial Virus

RSV is the leading viral agent causing severe respiratory tract disease worldwide in older adults. RSV is a non-segmented, negative-sense single stranded enveloped ribonucleic acid (RNA) virus. It is generally thought that the host immune response and viral damage both contribute to RSV disease pathogenesis. RSV may result in both upper and lower respiratory tract disease, but RSV infection results in more LRTD than other respiratory viruses. The burden of severe disease is at the extremes of life in early infancy and in older adults. While disease incidence varies from season to season and between settings, LRTD incidence in older adults is estimated to be 25/10 000 (1). Incidence data from this population is still relatively sparse compared to data from children, but incidence rates for emergency room visits and office visits, which could also serve as a proxy for LRTD, range from 0.27% to 1.19% (2) (3). Most individuals will have encountered the virus within the first year of life.

There is a medical need to improve patient quality of life by preventing LRTD. In the US, RSV contributes to approximately 177 000 hospitalizations and 14 000 deaths annually in individuals 65 years of age and older (4). Hospitalizations for RSV in older adults typically lasts 3 to 6 days with substantial proportions requiring intensive care unit (ICU) admission and mechanical ventilation. Among older adults hospitalized with RSV in the US, the mortality rate ranged between 6% and 8%, depending on studies, over the 2000-2016 period (5). The economic and clinical burden placed on the healthcare system during the RSV season will remain high until a preventative treatment option becomes available.

mRNA Vaccine Development

mRNA vaccines have the potential to be a promising alternative to conventional vaccine development approaches and could bring significant advantages over traditional vaccines. These advantages include 1) rapid development of new targets; 2) cell-free without infectious elements used in the manufacturing process; 3) shorter manufacturing time, facilitating rapid response to strain changes and pandemic emergencies; and 4) potential to include multiple immunogens. The authorization and use of the first mRNA vaccines for prevention of coronavirus disease 2019 (COVID-19) from Pfizer Inc. and Moderna, Inc., underscore the potential for this platform technology for vaccine development. Once the antigen of choice from the targeted pathogen has been identified, the antigen's gene is sequenced, synthesized, cloned into a deoxyribonucleic acid (DNA) template plasmid, and the mRNA is then produced by *in vitro* transcription (6). Once delivered into the person, the mRNA is translated into the corresponding antigen by the host cell machinery, allowing induction of both potent humoral and cellular immune response. The fully synthetic nature of mRNA vaccines allows for the rapid development of virtually any antigen sequence, including those for new emerging targets, and the capacity to include multiple antigens in the same vaccine.

mRNA molecules are too large and negatively charged to passively cross the cell membrane and are prone to nuclease degradation (7). Therefore, mRNA vaccines need a delivery system into host cells. LNPs are the most promising and commonly used tools for *in vivo* mRNA delivery (8). LNPs are usually composed of 4 components: 1) an ionizable cationic lipid promoting

self-assembly in a circa 70 to 100 nm particle, encapsulating the mRNA and allowing its endosomal release; 2) a lipid-linked polyethylene glycol deposed preferentially on the LNP surface, which increases the half-life of the formulation and reduces protein absorption; 3) cholesterol acting as a stabilizing agent; and 4) natural phospholipids supporting the lipid bilayer of the structure (6) (9) (10). The mRNA LNP vaccines do not require additional adjuvant enhancement, as the LNP, in addition to the mRNA, also induces adjuvant-like immune signals. Furthermore, mRNA vaccines are only targeted for cytoplasmic delivery, circumventing the risk of genomic integration.

After the first demonstration of *in vivo* translation of mRNA-LNPs in mouse by Pardi et al (11), several nonclinical studies have shown that mRNA LNP vaccines are able to induce a durable and protective immune response against several infectious pathogens (12-16) (17) (18). It has also been shown that mRNA-LNP based vaccines may induce greater T cell responses than traditional vaccine technologies (14). For instance, immunization with hemagglutinin (HA) mRNA-LNPs induced antibody (Ab) responses against the HA stalk domain of influenza virus in mice, rabbits, and ferrets. This study demonstrated that the HA stalk-specific Ab responses are associated with protection from homologous, heterologous, and heterosubtypic influenza virus infection in mice (15). The mRNA HA vaccine has also been shown to induce robust germinal center and B cell responses and an increase in circulating H10-specific ICOS+ PD-1+ CXCR3+ T follicular helper (Tfh) cells, a population shown to correlate with high avidity Ab responses after seasonal influenza vaccination in humans (16).

The safety and immunogenicity of mRNA vaccines have been assessed in several clinical studies for various antigens, using different LNPs, including Phase I studies evaluating a multivalent modified mRNA vaccine containing 2 mRNA (human metapneumovirus [hMPV] / human parainfluenza virus type 3 [HPIV3]) (19), as well as monovalent modified mRNA vaccines encoding RSV-F protein (20), Chikungunya structural polyprotein (21), and full-length HA-H10 or HA-H7 protein from A/Jiangxi-Donghu/346/2013 (H10N8) or A/Anhui/1/2013 (H7N9) influenza strains, respectively (22). Phase I through Phase III studies have also been conducted to evaluate both modified and unmodified mRNA vaccines for prevention of coronavirus disease 2019 (COVID-19), encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (23) (24) (25) (26) (27). In the aforementioned studies, mRNA doses varied between 2 µg and 400 µg, with the smallest doses (2 µg to 1 µg) evaluated in a vaccine study using unmodified SARS-CoV-2 mRNA (27).

mRNA COVID-19 vaccines have been deployed globally and while, in general, have been well tolerated, mRNA COVID-19 vaccines have tended to have higher rates of reactogenicity compared to vaccines developed using other technologies (28) (29). Different factors related to the mRNA, including modification status, purity, and LNP composition, can impact the safety and reactogenicity profile. Consequently, one of the key questions in optimizing the mRNA platform is to find a balance between reactogenicity and efficacy.

Safety surveillance has shown a higher rate of hypersensitivity reaction observed in the post-marketing setting of SARS-CoV-2 mRNA vaccine than was observed with other vaccines (30), potentially due to PEG and polysorbate vaccine components, but still range within the occurrence of anaphylaxis following any vaccination (ranges from 1 – 10 per million doses distributed depending on the vaccine studied). In addition, myocarditis and pericarditis were observed after SARS-CoV-2 mRNA vaccination in the post-marketing settings (31). These are

noted as rare events, observed mainly after the second dose of the SARS-CoV-2 mRNA vaccines in young males (under 30 years of age), but cases have been reported in both older males and in females as well, and also following the first dose of mRNA vaccines.

RSV Vaccine Development

In May 2023, GSK plc received US FDA approval of an adjuvanted RSV pre-fusion F protein-based vaccine (Arexvy) for prevention of L TD caused by S in a dults ≥ 60 years of age. Approval was based on data from a multi-national Phase III pivotal trial (AReSVi-006) in which 24 966 adults aged 60 years and older were randomly assigned in a 1:1 ratio to receive a single IM dose of the bivalent RSVPreF3 OA (0.5 mL) vaccine or placebo. The median age of participants was 69.5 years, the majority were considered "fit" per baseline frailty status evaluation, and similar proportions of male and female participants were included. Approximately 39% of participants had coexisting conditions at baseline that are known to be associated with an increased risk of severe RSV disease. The results of this trial showed statistically significant and clinically meaningful overall efficacy of 82.6% (96.95% CI, 57.9-94.1) against RSV-LRTD in older adults. In addition, efficacy was 94.6% (95% CI, 65.9-99.9) in older adults with at least 1 underlying medical condition of interest. Efficacy against severe RSV-LRTD, defined as an RSV-associated LRTD episode preventing normal, everyday activities, was 94.1% (95% CI, 62.4-99.9). The vaccine was generally well tolerated with an acceptable safety profile. The most frequently observed solicited AEs (ie, ≥ 10%) were injection site pain, fatigue, myalgia, headache, and arthralgia. These were generally mild to moderate and transient (32).

Also in May 2023, Pfizer, Inc., received US FDA approval of a bivalent RSV pre-fusion F (RSVpreF) vaccine (ABRYSVO™), for the prevention of LRTD caused by RSV in individuals 60 years and older. ABRYSVO is unadjuvanted and composed of 2 pre-F proteins selected to optimize protection against RSV A and RSV B strains. Approval was based on an ongoing Phase III trial designed to evaluate a single IM injection of the RSVPreF vaccine at a dose of 120 µg (S subgr oups A and B, 60 µg each). At the time of a planned interim analysis, 34 284 participants aged 60 years and older had been randomized in a 1:1 ratio to receive either a single IM dose of the RSVPreF vaccine or placebo. The median age of participants was 67 years, and similar proportions of male and female participants were included; immunocompromised persons were excluded. The interim analysis showed that RSV-associated LRTD (with at least 2 signs or symptoms) occurred in 11 participants in the vaccine group (1.19 cases per 1000 person-years of observation) and 33 participants in the placebo group (3.58 cases per 1000 person-years of observation) (vaccine efficacy, 66.7%; 96.66% CI, 28.8 – 85.8); 2 cases (0.22 cases per 1000 person-years of observation) and 14 cases (1.52 cases per 1000 person-years of observation), respectively, occurred with at least 3 signs or symptoms (vaccine efficacy, 85.7%; 96.66% CI, 32.0-98.7). RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group (2.38 cases per 1000 person-years of observation) and 58 participants in the placebo group (6.30 cases per 1000 person-years of observation) (vaccine efficacy, 62.1%; 95% CI, 37.1-77.9). Safety analyses showed that the incidence of local reactions was higher with vaccine (12%) than with placebo (7%), and the incidences of systemic events were similar (27% and 26%, respectively). Similar rates of adverse events through 1 month after injection were reported (vaccine, 9.0%; placebo, 8.5%), with 1.4% and 1.0%, respectively, considered by the investigators to be injection-related. Severe or life-threatening adverse events were reported in 0.5% of vaccine

recipients and 0.4% of placebo recipients. Serious adverse events were reported in 2.3% of participants in each group through the data-cutoff date (32).

In July 2023, Moderna, Inc., announced that it has submitted marketing authorization applications for its investigational RSV vaccine, mRNA-1345, with the European Medicines Agency, Swissmedic, and the Therapeutic Goods Administration in Australia. The company has also initiated a rolling submission of a Biologics License Application to the US FDA for mRNA-1345. The applications are based on resulted from a pre-specified interim analysis of the pivotal ConquerRSV study, a randomized, double-blind, placebo-controlled study of approximately 37 000 adults aged 60 years or older across 22 countries. The primary efficacy endpoints were based on 2 definitions of RSV-LRTD, defined as either 2 or more symptoms or 3 or more symptoms of disease. The trial met both its primary efficacy endpoints, with a vaccine efficacy (VE) of 83.7% (95.88% CI: 66.1%, 92.2%; $p < 0.0001$) against RSV-LRTD as defined by 2 or more symptoms, and a VE of 82.4% (96.36% CI: 34.8%, 95.3%; $p = 0.0078$) against RSV-LRTD defined by 3 or more symptoms. The vaccine was well tolerated with a favorable safety profile. Most solicited adverse reactions were mild or moderate, and the most commonly reported solicited adverse reactions in the mRNA-1345 group were injection site pain, fatigue, headache, myalgia, and arthralgia (33).

RSV mRNA Vaccine Candidate

The vaccine candidate that will be evaluated in this VAE00010 study is an mRNA LNP-based investigational vaccine consisting of a mRNA encoding the RSV pre-fusion (pre-F) antigen in one of 2 LNPs to be tested. The surface of the RSV virion contains 4 proteins: the attachment glycoprotein (G), the fusion protein (F), the matrix protein (M), and the small hydrophobic (SH) protein. The F protein enables fusion of the virus with the membrane of respiratory cells, making it essential for viral viability. Nonclinical data from *in vitro* and *in vivo* assays supported [redacted] as the antigen for entry into clinical trials. In pre-immune non-human primates (NHP) immunized with RSV-F protein subunit, [redacted] response was focused on the potent neutralizing antibodies (nAb) to antigenic site Ø. As pre-fusion-specific antibodies (Ab) are most potent, the [redacted] antigen may potentially trigger a high quality nAb response in the primed older adult population.

Two LNP formulations differing in their ionizable cationic lipid are being evaluated in this study: [redacted] (non-biodegradable) and [redacted] (biodegradable). These LNPs were selected based upon data from nonclinical studies. LNP [redacted] and LNP [redacted] had the highest expression of protein in studies completed in mice and NHPs and the highest nAb and nAb/enzyme-linked immunosorbent assay (ELISA) ratio (at least 10-fold higher) in comparison to the benchmark LNP (MC-3). With respect to safety, LNP containing [redacted] was assessed in a dose range finding toxicity study in rabbits following single IM administration (NOAEL of [redacted] µg) and in a pivotal repeated dose toxicity study in rabbits to support COVID-19 vaccine development (top dose of [redacted] µg being the tolerated safe dose). The higher *in vivo* expression, together with the preclinical immunogenicity and nonclinical safety data observed after repeated administrations support the selection of LNP containing [redacted] for the RSV mRNA vaccine clinical development.

An LNP containing [redacted] was assessed in a pivotal repeated dose toxicity study in rabbits following 3 IM administrations 3 weeks apart (Days 1, 22, and 43). The top dose level tested in

this study was [redacted] µg mRNA/dose ([redacted] µg), higher than the maximum intended clinical dose level of [redacted] µg mRNA/dose in Stage 1 of the VAE00010 trial. This design is considered supportive of the VAE00010 trial where healthy adults > 60 years of age are administered 1 or 2 IM injections of the RSV mRNA vaccine. Taken with the nonclinical safety data observed after repeated administrations, the results of this study supported the selection of LNP containing [redacted] for the RSV mRNA vaccine dose in Study VAE00010.

Overall, the available nonclinical immunogenicity and safety data support the use of the RSV mRNA vaccine candidate formulations (RSV mRNA LNP [redacted] and RSV mRNA LNP [redacted]) in humans as intended in study VAE00010. Further details on the nonclinical immunogenicity and safety assessments of the RSV mRNA vaccine candidate may be found in the Investigator's Brochure (IB).

The study intervention formulation and LNP for the study Phase IIa dose-ranging stage (Stage 2) was chosen based on results determined from Day 29 interim analysis of the Phase I/IIa (Stage 1) Main Cohort. In this interim analysis, higher doses of mRNA ([redacted] µg) + [redacted] showed higher immunogenicity; IgG results correlated with the RSV A neutralizing Ab responses, with higher titers and fold-rises in the same group. Safety data showed that all RSV mRNA formulations were generally well tolerated. Between the 2 tested LNPs, [redacted] showed a trend of better reactogenicity compared with [redacted], in particular for injection site pain and myalgia, which were the most frequently reported solicited reactions. These reactions were generally mild to moderate in severity, with few Grade 3 reactions. Unsolicited AEs were overall balanced across mRNA intervention groups, and no dose response was observed. Increases from baseline in Troponin I levels seen at D08 in 5 participants in the mRNA intervention groups were considered not clinically meaningful. There were no AESIs, no deaths, and few SAEs reported up to 28 days after vaccination. One participant in the mRNA/LNP [redacted] (low dose) group reported a related SAE due to an asymptomatic rise in high sensitivity troponin 8 days after vaccination. This isolated high troponin value experienced in a 61-year-old male participant was diagnosed as asymptomatic myocardial injury (adjudicated by Cardiac Adjudication Committee as "Other Cardiac ascular events, Acute myocardial injury)". This participant had no cardiac history or known risk factors for myocarditis (apart from sex and age). However, he had a long hike the day before troponin I testing for which strenuous exercise is known as a potential cause of troponin increase, and his family history included father with coronary artery bypass graft and mother with stents and pacemaker. The participant remained asymptomatic, stable, with fairly rapid fall of troponin value and no other AEs were reported. He recovered without sequalae. Considering time to onset, uncertainties on causes of this isolated troponin increase, and limited current knowledge on this RSV mRNA [redacted] vaccine, Sanofi conservatively assesses this event as related to the study vaccine even if there are suspicions of underlying conditions leading to this asymptomatic myocardial injury.

[redacted]

In Stage 1 (Phase I/IIa) of this current VAE00010 study, the [redacted] µg of S pr e-F mRNA with LNP [redacted] showed the highest immune response with an acceptable safety profile. Based on safety data from Phase I/IIa (Stage 1), and considering that higher immune responses were observed with the higher mRNA concentrations in Phase I/IIa, it could then be expected that increasing the dose would provide a better immune response with similar safety findings. Therefore, Stage 2, Phase IIa dose-ranging is proposed for evaluation of safety and immunogenicity of a higher dose (ie, [redacted] µg) of RSV pre-F mRNA with LNP [redacted]

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected AEs, the potential risks, and uncertainties of the RSV mRNA vaccine may be found in the IB

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 5.

Table 5: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: RSV mRNA Vaccine		
Anaphylaxis Refer to the IB for more information regarding the components of the vaccine	Important potential risk. All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine.	Participants at increased risk will be excluded from the study (see Section 5.2). Observation period after vaccination for early detection and treatment. Addressed in IB (administration precautions, potential adverse events), defined AESI in the trial (See Section 8.4.6).
Non-adverse safety observation in pancreas and lacrimal glands (from an animal study) Refer to the IB for more information	In the repeated dose toxicity study conducted in rabbits, reversible histopathological findings were observed in exocrine pancreas and lacrimal glands. Although the implications of these findings cannot be established at this time, these observations were of low severity, with no correlating clinical signs, no ocular abnormalities including absence of histologic changes in the cornea, were not associated with inflammation, and no impact on the physiological function. They were considered unlikely to lead to clinical symptoms in humans, especially after single administration. These findings were not observed in the biodistribution study in rabbits after single administration of the same lot at [redacted] µg mRNA/injection ([redacted]).	During the informed consent process, the participants enrolling in the study are informed about the necessity of reporting any health issue, even if they consider it is not related to the vaccine. All AEs reported during the study will be monitored by the SMT.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Injection site reactions and systemic reactions Refer to the IB for more information	Potential adverse reactions are expected to be similar to those observed for the mRNA vaccines assessed in different clinical studies; generally, injection site pain was the most commonly experienced injection site reaction, while headache, fatigue, myalgia, arthralgia, and chills were the most commonly experienced solicited systemic reactions.	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions, the need to attend the clinic if they are unwell, and the possibility to take analgesic / antipyretic drug.
Myocarditis, pericarditis, and/or myopericarditis Refer to the IB for more information	Potential risk based on the risk identified from post-marketing surveillance of SARS-CoV-2 mRNA vaccines. These are very rare events, observed in greatest numbers in males under the age of 30 years following a second dose of mRNA vaccines, but cases have been reported in both older males and in females as well, and also following the first dose of mRNA vaccines. It is unknown whether this risk could be linked to the mRNA technology or to the SARS-CoV-2 antigen (increased risk of myocarditis and pericarditis has also been identified following natural SARS-CoV-2 infection and after administration of non-mRNA SARS-CoV-2 vaccine).	The Phase I/IIa Sentinel Cohort of this study will include healthy adults between 18 to 50 years of age; the Phase I/IIa Main and Booster Cohorts and Phase IIa dose-ranging stage will include adults 60 years of age and older. Participants with a previous history of myocarditis and/or pericarditis will be excluded from the study (see Section 5.2). During the informed consent process, participants enrolling in the study will be informed of these potential risks and the need to contact the clinic if they are unwell. In **Phase I/IIa and in Phase IIa dose-ranging stage**, an ECG will be completed at Screening / Baseline, and findings consistent with probable or possible myocarditis, pericarditis, and/or myopericarditis will be considered as exclusion criteria (see Section 5.2). Participant will have an ECG in the event of symptoms potentially compatible with myocarditis and/or pericarditis. In addition, Troponin I will be tested pre- and post-vaccination to detect possible cases of myocarditis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		Study participants with symptoms compatible with potential myocarditis / pericarditis will be referred to consultation with a cardiologist or visit to the Emergency Department as applicable; a Cardiac Adjudication Committee will also evaluate such cases as specified in Section 8.4.6. Retention blood samples for safety evaluation may be used for testing of cardiac biomarkers. These events are AESIs and will be collected as specified in Section 1.3.
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (vaccine injection or blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia or seizure-like activity.	Observation period after blood sampling and vaccination for early detection and treatment.
Blood sampling will be performed throughout the study	There is a potential for bleeding, bruising, hematoma formation and infection at the venipuncture site.	Only appropriately qualified site personnel will obtain the blood draw.
Theoretical risk that participant can be exposed to SARS-CoV-2 infected individuals	SARS-CoV-2 infection is highly contagious. SARS-CoV-2 spreads through respiratory secretion or droplets. Transmission may also be possible via contaminated surfaces. Exposure can theoretically occur as a result of study procedures, including visits to the investigational sites and physical interactions with study staff.	Participant contact with other individuals when visiting study site (study site to set up system) should be minimized. Protective material (eg, masks and gowns) to be used in sites. Home visit option for completion of study procedures in the setting of containment measures to minimize exposure. Participants will also be advised to adhere to local regulations and guidance (eg, self-isolation, social distancing) to minimize risk of exposure to SARS-CoV-2 infected individuals.

Appropriate medical equipment and routine emergency medications must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. This equipment is not provided by the Sponsor.

2.3.2 Benefits from Study Participation

While the benefit and risks of the candidate vaccine formulation at the individual level are largely unknown, study participation and study conduct are considered fundamental from the societal perspective towards the goal of finding a vaccine to decrease individual and public health burden of LRTD due to RSV.

Participants will contribute to the process of developing a vaccine against RSV, a viral agent causing severe respiratory tract disease. They may benefit from access to medical evaluations / assessments associated with study procedures (eg, medical visits, physical exam, laboratory parameter assessment, etc.). Protection from disease caused by RSV as a result of vaccination with this investigational vaccine has not yet been demonstrated.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, there is no unreasonable or significant risk of illness or injury for the participants.

3 Objectives and Endpoints

3.1 Stage 1 (Phase I/IIa)

The study objectives and the corresponding endpoints for Phase I/IIa are described in Table 6.

Table 6: Objectives and endpoints (Phase I/IIa)

Objectives	Endpoints
Primary	
Safety Objective To assess the safety profile 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]	***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 and MAAEs reported up to 28 days after vaccination

Objectives	Endpoints
	• 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
Immunogenicity Objectives 1) To assess the durability of immune response at 3, 6, and 12 months following primary vaccination on D01	***Immunogenicity Endpoints*** <u>Endpoints for objective #1</u>: • 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

Objectives	Endpoints
2) To assess the durability of the immune response following booster vaccination 12 months after the primary vaccination, in a subset of participants	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]
[redacted]	[redacted]

3.2 Stage 2 (Phase IIa dose-ranging)

The study objectives and the corresponding endpoints for Phase IIa dose-ranging stage are described in Table 7.

Table 7: Objectives and endpoints (Phase IIa dose-ranging)

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-vaccination (D29)
Secondary	
Immunogenicity Objective To assess the immune response at 28 days following vaccination on D01	***Immunogenicity Endpoint*** Serum anti-F immunoglobulin G (IgG) Ab titers at pre-vaccination (D01) and 28 days (D29) post-vaccination

4 Study Design

4.1 Overall Design

The design of the study Stage 1 (Phase I/IIa) and Stage 2 (Phase IIa dose-ranging) are summarized in the following Sections 4.1.1 and 4.1.2, respectively.

4.1.1 Stage 1 (Phase I/IIa)

The design of the study Phase I/IIa is summarized in Table 8.

Table 8: Overall design (Phase I/IIa)

Type of design	Sequential (Phase I)/ parallel, multi-center (Phase IIa)
Phase	I/IIa
Control method	Placebo-controlled
Study population	Healthy adults 18 to 50 years, and 60 years of age and older
Level and method of blinding	Sentinel Cohort: Single-blind • Investigators, laboratory personnel, and participants will be blinded • 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 and Booster Cohorts: Modified double-blind • Investigators, laboratory personnel, Sponsor study staff, and participants will be blinded • Sponsor study staff preparing/administering the study interventions will be unblinded • Safety data will be reviewed in a blinded manner by the Sponsor 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
Investigational 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 9 and Table 10, respectively). Approximately 200 participants from the Main Cohort will be enrolled in the Booster Cohort (see Table 11). 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 was performed in a stepwise manner, based on the favorable ESDRs by an internal SMT. Refer to Section 8.4.9 and also Figure 4 for details on sequential enrollment and ESDRs. Starting with the low dose formulations, and for each of the 3 dose-levels, eligible participants were 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 9) Main Cohort: Enrollment of the Main Cohort proceeded after completion of a cumulative ESDR from the Sentinel Cohort. 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 10) 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 11)
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	Phase I/IIa: SMT, SERT, PSB, CAC (see Section 10.1.5)

Table 9: 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

LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; N/A: not applicable; RSV: respiratory syncytial virus; SC: Sentinel Cohort

Table 10: 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

LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; N/A: not applicable; RSV: respiratory syncytial virus

Table 11: Planned sample size for the 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.

4.1.2 Stage 2 (Phase IIa dose-ranging)

The design of the study Phase IIa dose-ranging stage is summarized in Table 12.

Table 12: Overall design (Phase IIa dose-ranging)

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 13)
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 based on the study evolution)
Use of an Independent Data Monitoring Committee, Dose-Escalation Committee, or similar review group	Phase IIa dose-ranging: SMT, CAC (see Appendix 10.1.5)

Table 13: Planned sample size for Phase IIa dose-ranging (participants aged 60 years and older)

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

4.2 Scientific Rationale for Study Design

Rationale for participant age and the need for an RSV vaccine in the target population

The population of older adults was selected as there is a medical need to improve patient quality of life by preventing respiratory disease associated with RSV in adults aged ≥ 60 years. The severity of RSV is higher in the older adult population, and with a growing older adult population

in industrialized countries, there is a significant need for the development of a safe and effective RSV vaccine (34). Severe disease and hospitalization rates associated with RSV could likely be reduced in this susceptible population via vaccination.

Rationale for study design

The RSV mRNA vaccine candidate is being developed for the prevention of LRTD caused by RSV in adults 60 years of age and older. This study has 2 stages: Stage 1 (Phase I/IIa), designed to primarily evaluate the safety and immunogenicity of 3 dose-levels of an RSV mRNA vaccine candidate with 2 different LNP-based formulations (ie, an LNP containing [redacted] or [redacted], and Stage 2 (Phase IIa dose-ranging), designed to evaluate the safety and immunogenicity of the proposed mRNA vaccine candidate.

Stage 1 of the study included a Sentinel Cohort in healthy adults aged 18 to 50 years to evaluate the safety of each dose level and LNP formulation as no prior clinical safety data has been established for an LNP that contains [redacted]. Prior clinical safety data have been established with [redacted]. The primary objective of this stage is to assess the frequency and severity of vaccine-related solicited adverse events/reactions, as well as unsolicited AEs, AESIs, and SAEs. The vaccine-induced neutralizing antibodies 28 days post-vaccination will also be assessed. This stage is also designed to assess durability of the immune response and the safety and immune response of a booster vaccination. An annual booster vaccination may be needed to enhance immune response. An exploratory Booster Cohort has been included in this stage to evaluate the safety of re-vaccination and the immune response of participants administered a booster vaccination 12 months after the primary vaccination. Assessments of antibody titers up to 12 months post-booster vaccination will aid in assessing how rapidly Ab titers can be regained, and persistence of the immune response after the booster vaccination.

Stage 1 also includes an [redacted] considering that the study is being conducted during the 2022-2023 RSV Northern hemisphere season (35). Stage 1 is also intended to select the vaccine dose and LNP formulation to be used in Stage 2 of the study, based on adequate safety and immunogenicity profiles. Stage 1 will be conducted in healthy adults aged 18 to 50 years, and 60 years of age or older, with active enrollment in the US, Puerto Rico, and Australia[a].

Stage 2 of the study is a Phase IIa, placebo-controlled, dose-ranging stage designed to evaluate the safety and immunogenicity of the RSV mRNA vaccine. Doses of [redacted] µg and [redacted] µg will be used in Stage 2.

Rationale for unblinding/blinding in the 2 stages

In Stage 1 (Phase I/IIa), and as a safety precaution, the enrollment of participants and dose-escalation was performed in a stepwise manner based on successful safety reviews by an internal, unblinded Sponsor SMT. There was an ESDR of data from at least 20 participants having safety data for 7 days post-vaccination of the investigated dose-level prior to enrolling participants in the subsequent dose-level of the Sentinel Cohort. Enrollment was paused before each dose-escalation in the Sentinel Cohort. Enrollment began for the subsequent cohorts if no pre-specified alert thresholds occurred, or if investigations by the SMT concluded that there was no

[a] It is to be noted that the list of participating countries may be modified based on the study evolution.

unreasonable and significant risk for study participants. If the SMT determined that there is a tolerability or safety concern with a particular dose level, higher doses of that investigational vaccine would not have been evaluated in the Sentinel Cohort. This dose level and any higher dose levels would also have been excluded from evaluation in the Main Cohort. A cumulative review of the safety data from the Sentinel Cohort was completed prior to enrolling participants in the Main Cohort, with enrollment depending upon a favorable safety review by the SMT. A SERT from the Sponsor (but independent of the study) will review safety data in an unblinded manner if recommended by Safety Governance. The remaining Sponsor study team will remain blinded.

In Stage 2 (Phase IIa dose-ranging), multiple safety analyses will be performed. Safety data will be reviewed in both blinded and unblinded manners by the SMT. Sponsor SMT will review an unblinded safety analysis after 7 days of safety data are available for all participants in the study intervention groups and after 28 days of safety data are available.

Rationale for placebo

Placebo will be used to allow safety comparisons with the study intervention vaccine. The inclusion of a placebo group will maintain the study blind and will allow for an unbiased evaluation of clinical outcomes by study intervention group.

4.3 Justification for Dose

Phase I/IIa (Stage 1)

The selection of the dose levels ([redacted], [redacted], or [redacted] µg) and LNP formulations for the S m NA vaccine candidates being evaluated in this study are based upon data from nonclinical safety and immunogenicity studies along with data generated with other mRNA vaccines in nonclinical and clinical studies.

Nonclinical studies have indicated erythropoietin expression, as well as influenza mRNA immunogenicity in mice and non-human primates (NHPs), to be similar or higher with the LNP containing [redacted], the LNP proposed in this study, compared to the MC3 LNP utilized as a benchmark for potency for this range. This suggests that the potency of the proposed LNP is likely to be at least comparable to that of MC3. MC3 has been utilized as the LNP in studies evaluating pandemic influenza vaccine candidates (36), and showed immune responses with doses of [redacted] µg to [redacted] µg of mRNA.

[redacted]

[redacted]. This study will be conducted under Good Laboratory Practice (GLP) compliance with full set of parameters assessed as mentioned in the World Health Organization (WHO) guidelines to evaluate the systemic and local tolerance of the vaccine.

Phase IIa dose-ranging (Stage 2)

The study intervention formulation and LNP for the study Phase IIa dose-ranging stage (Stage 2) was chosen based on results determined from Day 29 interim analysis of the Phase I/IIa (Stage 1) Main Cohort. These results indicated that higher doses of mRNA ([redacted] µg) + [redacted] showed higher immunogenicity; IgG results correlated with the RSV A neutralizing Ab responses, with higher titers and fold-rises in the same group. Safety data showed that all RSV mRNA formulations were generally well tolerated. Between the 2 tested LNPs, [redacted] showed a trend of better reactogenicity compared with [redacted], in particular for injection site pain and myalgia, which were the most frequently reported solicited reactions.

During Stage 1, the [redacted] µg dose of RSV mRNA vaccine combined with the selected LNP ([redacted]) showed the highest immune response with a favorable safety profile; it is expected that the [redacted] µg dose of RSV mRNA vaccine with the selected LNP will show a better immune response.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last contact planned in the SoAs.

The end of the study is defined as the date that the last test results have been released for samples collected at the last sample collection visit related to primary and secondary endpoints. The end of the study much be achieved no later than 9 months after the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

5.1.1 Stage 1 (Phase I/IIa)

5.1.1.1 Inclusion Criteria to be Checked at Screening

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Sentinel Cohort: Aged 18 to 50 years on the day of inclusion

Main Cohort: Aged 60 years or older on the day of inclusion[a]

Sex, contraceptive/barrier method and pregnancy testing requirements

I02: Sentinel Cohort: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile.

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration.

Main and Booster Cohorts: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile.

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Informed consent

I04: Informed consent form has been signed and dated

5.1.1.2 Inclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are eligible for the study only if all of the following criteria are met:

[a] "60 years of age or older" means from the day of the 60th birthday.

Age

I01:Sentinel Cohort: Aged 18 to 50 years on the day of inclusion

Main Cohort: Aged 60 years or older on the day of inclusion

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Sex, contraceptive/barrier method and pregnancy testing requirements

I05: Sentinel Cohort: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile.

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) before the first dose of study intervention.

Main and Booster Cohorts: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

5.1.2 Stage 2 (Phase IIa dose-ranging)

Inclusion Criteria to be Checked at Screening and at Visit 01 (Day 01)

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Aged 60 years or older on the day of inclusion[a]

Sex, contraceptive/barrier method and pregnancy testing requirements

I02: A female participant is eligible to participate if she is not pregnant or breastfeeding and:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

[a] "60 years of age or older" means from the day of the 60th birthday.

Other inclusion

I03: Able to attend all scheduled visits and to comply with all study procedures

Informed consent

I04: Informed consent form has been signed and dated

5.2 Exclusion Criteria

5.2.1 Stage 1 (Phase I/IIa)

5.2.1.1 Exclusion Criteria to be Checked at Screening

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[a] ; any allergic reaction (eg, anaphylaxis) after administration of mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[b] in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

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[a] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[b] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[a]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[d]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

E13: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E16: Self-reported or documented human immunodeficiency virus (HIV) detected by any FDA-approved / validated test, hepatitis B virus surface antigen (HBsAg), hepatitis B core antibodies (HBcAb), hepatitis C virus antibodies (HCV Abs), or positive SARS-CoV-2 RT-PCR or antigen test[b]

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

5.2.1.2 Exclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are not eligible for the study if any of the following criteria are met:

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[a] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

[b] Participants must not have had a positive SARS-CoV-2 RT-PCR or antigen test or self-reported COVID-19 in the 10 days prior to the visit; a prospective participant should not be included in the study until the condition has resolved. A diagnostic test for SARS-CoV-2 is not mandatory for screening. Investigators may perform screening SARS-CoV-2 testing at their discretion.

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[a]; any allergic reaction (eg, anaphylaxis) after administration of mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[b] in the 3 weeks preceding inclusion, contraindicating IM injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[d]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[a]

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[a] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[b] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[d] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

E13: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

E18: Participants with a Screening electrocardiogram that is consistent with possible myocarditis, pericarditis, and/or myopericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E19: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E20: Any screening laboratory parameter with laboratory abnormalities that are greater than Grade 1 or deemed clinically significant in the opinion of the investigator

If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.2.2 Stage 2 (Phase IIa dose-ranging)

<u>Exclusion Criteria to be Checked at Screening</u>

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study

interventions used in the study or to a product containing any of the same substances[a]; any allergic reaction (eg, anaphylaxis) after administration of mRNA vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

E06: Bleeding disorder, or receipt of anticoagulants[b] in the 3 weeks preceding inclusion, contraindicating IM injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[d]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[a]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

---

[a] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[b] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[d] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E16: Self-reported or documented human immunodeficiency virus (HIV) detected by any FDA-approved / validated test, hepatitis B virus surface antigen (HBsAg), hepatitis B core antibodies (HBcAb), hepatitis C virus antibodies (HCV Abs), or positive SARS-CoV-2 RT-PCR or antigen test[a]

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

Exclusion Criteria to be Checked at Visit 01 (Day 01)

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[b]; any allergic reaction (eg, anaphylaxis) after administration of mRNA COVID-19 vaccine

E03: History of RSV-associated illness, diagnosed clinically, serologically, or microbiologically in the last 12 months

E04: Previous history of myocarditis, pericarditis, and/or myopericarditis

E05: Thrombocytopenia or bleeding disorder, contraindicating IM injection based on investigator's judgment

[a] Participants must not have had a positive SARS-CoV-2 RT-PCR or antigen test or self-reported COVID-19 in the 10 days prior to the visit; a prospective participant should not be included in the study until the condition has resolved. A diagnostic test for SARS-CoV-2 is not mandatory for screening. Investigators may perform screening SARS-CoV-2 testing at their discretion

[b] The components of study intervention(s) are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

E06: Bleeding disorder, or receipt of anticoagulants[a] in the 3 weeks preceding inclusion, contraindicating intramuscular injection

E07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[b]

E08: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E09: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[c]

E10: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[d]

E11: Previous vaccination against RSV with a licensed or investigational vaccine

E12: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

Prior/current clinical study experience

E14: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E15: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E17: Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

---

[a] Anticoagulants include, but are not limited to the following: warfarin, apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, unfractionated heparin (therapeutic dose), enoxaparin, dalteparin, fondaparinux, argatroban, and bivalirudin.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[c] If the participant is enrolled and seeks vaccination of an authorized influenza or non-mRNA COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. In the case of an mRNA COVID-19 vaccine, at the earliest 60 days after study vaccination and at any time thereafter. If the participant receives authorized influenza, COVID-19, or mRNA vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

E18: Participants with a Screening electrocardiogram that is consistent with possible myocarditis, pericarditis, and/or myopericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E19: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E20: Any screening laboratory parameter with laboratory abnormalities that are greater than Grade 1 or deemed clinically significant in the opinion of the investigator

E21: Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study before the end of the study or planning participation in strenuous or endurance exercise through V03.

If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. Screening information is recorded in the source documents.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information to be reported in the CRF includes demography, screen failure details, eligibility criteria not met, and any SAE.

<u>For Stage 1 (Phase I/IIa):</u>

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened if failure is related with safety laboratory results. In this case the principal investigator could repeat the safety laboratory tests as long as the recruitment period is active for a specific cohort.

<u>For Stage 2 (Phase IIa dose-ranging):</u>

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened. Such a participant should be provided with a different participant number.

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention

The Sponsor may decide to temporarily delay the enrollment/randomization/administration of study intervention in case of occurrence of an event requiring further investigation and until the Sponsor's governance decision on further steps. For example, SMT is empowered to recommend a precautionary intervention delay during investigation of events reaching alert threshold or other clinically significant potential adverse reactions identified from signal detection activities. In addition, enrollment and administration of the study intervention will be temporarily delayed if pausing rules are met (refer to Section 8.4.10.2). After investigation, the SMT will decide whether the enrollment/randomization/administration of the study intervention can be resumed if criteria are met (refer to Section 8.4.10.2).

6 Study Interventions and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational/auxiliary medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to study participants during the study conduct.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.9). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 Study Interventions Administered

6.1.1 Stage 1 (Phase I/IIa)

Study interventions, in greater detail, are described in Table 14.

Table 14: Identity of study interventions (Phase I/IIa)

Intervention Name	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**Placebo**
Intervention Description	RSV pre-F mRNA in an LNP containing [redacted] or [redacted]: low dose ([redacted] µg), medium dose ([redacted] µg), or high dose ([redacted] µg)						
Marketing authorization status	Not approved						Not applicable
Study Groups	Group 1 (Sentinel and Main Cohorts)	Group 2 (Sentinel and Main Cohorts)	Group 3 (Sentinel and Main Cohorts)	Group 4 (Sentinel and Main Cohorts)	Group 5 (Sentinel and Main Cohorts)	Group 6 (Sentinel and Main Cohorts)	Group 7 (Sentinel, Main, and Booster Cohorts)
	Group 1, 2, 3, 4, 5, or 6 (Booster Cohort; study intervention, study group and unit dose strength to be determined at Interim Analysis)						
Use	Experimental						Placebo control
IMP or NIMP/AxMP	IMP						IMP
Type	Vaccine						Vaccine
Dosage Form	Liquid frozen solution in a vial						Liquid solution, in a vial
Unit Dose Strengths	Each [redacted] mL dose of study intervention after dilution will contain the following:						
	• RSV pre-F mRNA, low-dose ([redacted] µg) • LNP containing [redacted]	• RSV pre-F mRNA, low-dose ([redacted]µg) • LNP containing [redacted]	• RSV pre-F mRNA, medium-dose ([redacted] µg) • LNP containing [redacted]	• RSV pre-F mRNA, medium-dose ([redacted] µg) • LNP containing [redacted]	• RSV pre-F mRNA, high-dose ([redacted] µg) • LNP containing [redacted]	• RSV pre-F mRNA, high-dose ([redacted] µg) • LNP containing [redacted]	• [redacted]% normal saline

Intervention Name	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**RSV mRNA LNP [redacted]**	**Placebo**
	The study intervention will be formulated as a single dose of an mRNA-LNP complex and will be diluted to the required mRNA dose at the study site using a buffer diluent.						
Excipients/Diluent	Diluent: [redacted]x PBS (2°C to 8°C) Vaccine will be diluted with [redacted]x PBS at the study site according to dose preparation protocol						None
Dosage Level	[redacted] mL per dose						
Number of Doses/Dosing Interval	Sentinel and Main Cohort: 1 injection Booster Cohort: 2 injections; second injection administered 12 months post-primary injection						
Route of Administration	Intramuscular injection						
Site of Administration	Deltoid muscle in the upper arm						
Sourcing	Provided by the Sponsor						
Packaging and Labeling	Each study intervention will be provided in an individual box. Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the dose number. All will be labeled as required per country requirement.						
Current/Former Name(s) or Alias(es)	To be determined						
Batch Number	To be determined						
Storage Conditions	Study interventions will be stored at -80°C ± 10°C						Study interventions will be stored at a temperature ranging from 2°C to 8°C.

Abbreviations: IMP: Investigational Medicinal Product; LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; NIMP: Non-Investigational Medicinal Product; PBS: Phosphate buffered saline; RSV: respiratory syncytial virus

6.1.2 Stage 2 (Phase IIa dose-ranging)

Study interventions, in greater detail, are described in Table 15.

Table 15: Identity of study interventions (Phase IIb dose-ranging)

Intervention Name	**Unit dose strength and LNP**	**Placebo**
Intervention Description	RSV pre-F mRNA in an LNP containing [redacted]: [redacted] µg or [redacted] µg	
Marketing authorization status	Not approved	Not applicable
Study Groups	Group 0 ([redacted] µg), Group 1 ([redacted] µg)	Group 2
Use	Experimental	Placebo control
IMP or NIMP/AxMP	IMP	IMP
Type	Vaccine	Vaccine
Dosage Form	Liquid frozen solution in a vial	Liquid solution, in a vial
Unit Dose Strength	[redacted] µg or [redacted] µg of RSV pre-F mRNA in an LNP containing [redacted]	[redacted] normal saline
Excipients/Diluent	Diluent: PBS [redacted] (2°C to 8°C) Vaccine will be diluted with [redacted]x PBS at the study site according to dose preparation protocol	None
Dosage Level	[redacted] mL per dose	
Number of Doses/Dosing Interval	1 injection	
Route of Administration	Intramuscular injection	
Site of Administration	Deltoid muscle in the upper arm	
Sourcing	Provided by the Sponsor	
Packaging and Labeling	Each study intervention will be provided in an individual box. Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the dose number. All will be labeled as required per country requirement.	
Current/Former Name(s) or Alias(es)	To be determined	
Batch Number	To be determined	
Storage Conditions	Study interventions will be stored at -80°C ± 10°C	Study interventions will be stored at a temperature ranging from 2°C to 8°C.

Abbreviations: IMP: Investigational Medicinal Product; LNP: lipid nanoparticle; mRNA: messenger ribonucleic acid; NIMP: Non-Investigational Medicinal Product; PBS: Phosphate buffered saline; RSV: respiratory syncytial virus

6.2 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.
3) All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4) The investigator, institution, or the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5) Further guidance and information for the final disposition of unused study interventions will be provided to the study personnel.

6.3 Assignment to Study Intervention

6.3.1 Stage 1 (Phase I/IIa)

Participants who sign the informed consent form (ICF) at Screening and meet the eligibility criteria at Screening and at Visit 01 will be randomly assigned to one of the study intervention groups at Visit 01, according to the cohort:

- Sentinel Cohort 1: RSV mRNA vaccine at low dose with LNP [redacted], RSV mRNA vaccine at low dose with LNP [redacted], or placebo in a 1:1:1 ratio
- Sentinel Cohort 2: RSV mRNA vaccine at medium dose with LNP [redacted], RSV mRNA vaccine at medium dose with LNP [redacted], or placebo in a 1:1:1 ratio
- Sentinel Cohort 3: RSV mRNA vaccine at high dose with LNP [redacted], RSV mRNA vaccine at high dose with LNP [redacted], or placebo in a 1:1:1 ratio
- Main Cohort: RSV mRNA vaccine at low dose with LNP [redacted], RSV mRNA vaccine at low dose with LNP [redacted], RSV mRNA vaccine at medium dose with LNP [redacted], RSV mRNA vaccine at medium dose with LNP [redacted], RSV mRNA vaccine at high dose with LNP [redacted], RSV mRNA vaccine at high dose with LNP [redacted], or placebo in a 1:1:1:1:1:1:1 ratio

At Visit 01, randomization will be stratified by cohort (Sentinel Cohort 1, 2, 3 or Main Cohort), by CMI subset (Yes or No), and by Japanese origin status (Yes or No).

Participants from the placebo group and the selected formulation group (ie, both the dose-level and the LNP formulation) of the Main Cohort will be eligible to receive a booster dose 12 months after the first vaccination. At Visit 08, participants who meet the eligibility criteria, including the booster screening visit (Screening V08), will be randomly assigned in a 1:1 ratio to receive the RSV mRNA vaccine selected formulation or placebo.

At Visit 08, randomization will be stratified by the study intervention group randomized at Visit 01.

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. The IRT will also state whether the participant has been assigned to the CMI subset (ie, 20 participants of each study intervention group of the Main Cohort, recruited from a limited number of selected sites). The full detailed procedures for group allocation are provided separately. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT.

6.3.2 Stage 2 (Phase IIa dose-ranging)

Participants who sign the informed consent form (ICF) and meet the eligibility criteria at Screening (as applicable) and Visit 01 will be randomly assigned in a 1:1:1 ratio to the RSV mRNA vaccine candidate [redacted] µg or [redacted] µg, or placebo.

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. The full detailed procedures for group allocation are provided separately. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT.

6.4 Blinding

Stage 1 (Phase I/IIa)

During the Stage 1 Sentinel Cohort (Phase I/IIa), the study will be performed in a single-blind fashion:

- Investigators, study staff who conduct the safety assessment, and the participant will not know which study intervention is administered
- Sponsor study staff will be unblinded, as well as the study staff who prepare and administer the study intervention and are not involved with the safety evaluation will know which study intervention is administered

Safety data will be reviewed in an unblinded manner by the Sponsor Safety Management Team (SMT) during the Sentinel Cohort (eg, SMTs for all ESDRs, any planned or ad hoc SMT).

During the Main and Booster Cohorts (Phase I/IIa), safety data will be reviewed in a blinded manner by the SMT until the code is broken for the Sponsor for the planned interim analysis.

Once the code is broken, safety data will be reviewed in an unblinded manner for the Booster Cohort.

- An internal SERT, independent of the study team, will review unblinded data during the study if recommend by Safety Governance

Stage 2 (Phase IIa dose-ranging)

During Stage 2 (Phase IIa dose-ranging), the study will be performed in a modified double-blind fashion:

- 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 laboratory personnel) will be unblinded

The code may be broken in the event of an AE only when the identification of the study intervention received could influence the treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the AE.

The blind can be broken by the investigator or a designee through the IRT system. Once the emergency has been addressed by the site, the investigator or a designee must notify the Sanofi Pasteur MO if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking case report form (CRF) is to be completed.

The IEC / IRB must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in the Sponsor's files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made:

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for Harmonisation (ICH) E2A. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's study intervention or group assignment) will not be communicated to either the investigator or the immediate team working on the study, except for the GPV representative.

6.5 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 15 and Table 16), and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All study interventions will be administered by qualified and trained study personnel.
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose(s) given to each participant, and unused or wasted doses.

6.6 Dose Modification

Not applicable.

6.7 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.8 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the investigator/treating physician should:

1) Contact the RMO immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

6.9 Prior and Concomitant Therapy

Prior and concomitant therapy collected include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an AE) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)

  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.

- Medications impacting or that may have an impact on the immune response (eg, other vaccines, including an RSV vaccine, blood products, antibiotic classes that may interfere with bioassays used by Sanofi Pasteur laboratory or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Reportable medications will be collected in the CRF until the end of the solicited and unsolicited follow-up period, as described in the SoAs (Section 1.3).

Dosage and administration route, homeopathic medication, topical steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention).

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belong(s) to the reportable medications list. Medications will be coded using the WHO Drug dictionary.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.9.

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications – Stage 1 (Phase I/IIa) Booster Cohort only

Should a participant experience one of the conditions listed below, the investigator will postpone further vaccination (ie, administration of the booster dose for participants eligible to be enrolled in the Booster Cohort) until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoAs.

TCI01: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[a]

TCI02: Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness/infection on the day of vaccination, according to investigator judgment

TCI03: Receipt of any vaccine other than mRNA vaccine in the 4 weeks preceding any study intervention administration or planned receipt of any vaccine other than mRNA vaccine in the 4 weeks following any study intervention administration[b]

TCI04: Receipt of any mRNA vaccine in the 60 days preceding any study intervention administration or planned receipt of any mRNA vaccine in the 60 days following any study intervention administration[b]

7.1.2 Definitive Contraindications – Stage 1 (Phase I/IIa) Booster Cohort only

Participants will permanently discontinue (definitive discontinuation) study intervention (ie, administration of the booster dose) for the reasons listed below. These participants will not be

[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, dementia, or chronic infection.

[b] If the participant is enrolled and seeks vaccination of an authorized influenza or COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. If the participant receives the authorized influenza or COVID-19 vaccine, this information will be collected. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures.

eligible to receive the booster dose. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience at least one of the conditions listed below, the investigator will discontinue vaccination:

DCI01: Pregnancy, as indicated by a positive urine test

DCI02: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

DCI03: Abnormal laboratory parameter of Grade 2 or 3 and assessed by the investigator as related to the previous dose of vaccine

DCI04: SAE assessed as related to the study vaccine following the previous dose of vaccine, based on investigator's judgment

DCI05: Myocarditis, pericarditis, and/or myopericarditis

DCI06: RSV-associated illness diagnosed clinically, serologically or microbiologically

DCI07: Thrombocytopenia or bleeding disorder

DCI08: Chronic illness (eg, cardiac disorders, renal disorders, autoimmune disorder, diabetes, psychiatric disorder, or chronic infection) that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion

DCI09: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

DCI10: Receipt of anticoagulants in the 3 weeks preceding booster injection

DCI11: Receipt of immune globulins, blood, or blood-derived products in the past 3 months

DCI12: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the pre-booster vaccination blood draw at V07 (BL0005)

DCI13: Participation in or plans to participate in another clinical study investigating a vaccine, drug, medical device, or medical procedure during the booster phase of the study

DCI14: Self-reported or documented seropositivity for human immunodeficiency virus (HIV) antigen and/or Abs, hepatitis B virus surface antigen (HBsAg), hepatitis B core antibodies (HBcAb), or hepatitis C virus antibodies (HCV Abs)

In the event of a local or national immunization program with a pandemic influenza vaccine or any other vaccine as needed, participants who receive that vaccine at any time during the study will not be withdrawn from the study.

For Stage 2 (Phase IIa dose-ranging): As this is a single dose study stage, definitive contraindications (ie, definitive discontinuation of study intervention) is not applicable.

7.1.3 Other Reasons

A participant may discontinue from study intervention at any time at the participant's own request for any reason (or without providing any reason).

A participant may discontinue from study intervention at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants should continue to be followed for safety.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason)
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, or compliance reasons
- The reason for withdrawal should be clearly documented in the source documents and in the CRF
- The participant will be permanently discontinued from the study intervention and the study at that time. However, the site should attempt to contact the participant and complete all scheduled safety follow-ups, except if the participant specified that they do not want to be contacted again and it is documented in the source document
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested (unless local law requires not to destroy them), and the investigator must document this in the site study records
- Withdrawn participants will not be replaced

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and the participant is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or if the participant cannot be contacted as planned in the SoAs:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record

- Should the participant continue to be unreachable, the participant will be considered lost to follow-up

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoAs. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA tables (Section 1.3).
- Additional details on study procedures, sample management and handling, and investigational product management will be provided to sites separately. Sites will be trained on these procedures, with training documented, prior to study conduct.

8.1 Administrative and General Procedures

8.1.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF. In addition, history of receipt of mRNA-based vaccines will be recorded. Collected information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.1.2 Sample Collection

8.1.2.1 Stage 1 (Phase I/IIa)

Blood samples will be collected as described in the SoA tables (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study Phase I/IIa, including any extra assessments that may be required, will not exceed 233 mL (see Table 16, Table 17, and Table 18). The amount of blood collected at each visit will range from

15 mL to 50 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Guidance and information for the sample collection, preparation, storage, and shipment are provided separately.

Table 16: Blood sampling volume (mL) per visit – Sentinel Cohort Phase I/IIa (participants aged 18 to 50 years)

Visit Number (V) **Trial Timelines (Days [D] /Months [M])** **Time Windows (Days)**	**Screening** **-D14 to D01**	**V01** **D01**	**V02** **D04** **±1D**	**V03** **D08** **±1D**	**V04** **D29** **+ 7D**	**V05** **3M** **+14D**	**V06** **6M** **+ 14D**	**V07** **12M** **+ 28D**
Screening serology (HIV Ab, HBsAg, HBcAb, HCV Ab) (~5 mL)	X							
Clinical Safety Laboratory (approximately 15 mL at each timepoint)*	BS0001		BS0002	BS0003	BS0004			
Hematology, Coagulation, Serum Chemistry (see Table 22)	X		X	X	X			
Immunogenicity assessments (20 mL at each timepoint)		BL0001			BL0002	BL0003	BL0004	BL0005
RSV Anti-F IgG ELISA		X			X	X	X	X
RSV MN		X			X	X	X	X
Biobank Sampling (15 mL at each timepoint)		X			X	X	X	X
TOTAL (mL)	**20**	**35**	**15**	**15**	**35**	**35**	**35**	**35**

Abbreviations: BL: blood sample for immunogenicity; BS: blood sample for safety; ELISA: enzyme-linked immunosorbent assay; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibodies; HIV: human immunodeficiency virus; IgG: immunoglobulin G; MN: microneutralization; RSV: respiratory syncytial virus

* The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements

Table 17: Blood sampling volume (mL) per visit – Main Cohort Phase I/IIa (participants aged 60 years and older)

Visit Number (V) **Trial Timelines (Days [D]/Months [M])** **Time Windows (Days)**	**Screening** **D14 to - D01**	**V01** **D01**	**V02*** **D04** **±1D**	**V03** **D08** **+1D**	**V04** **D29** **+ 7D**	**V05** **3M** **+14D**	**V06** **6M** **+14D**	**V07** **12M** **+28D**
Screening serology (HIV Ab, HBsAg, HBcAb, HCV Ab) (~5 mL)	X							
Clinical Safety Laboratory (approximately 15 mL at each timepoint)†	BS0001			BS0002	BS0003			
Hematology, Coagulation, Serum Chemistry (see Table 22)	X			X	X			
Immunogenicity assessments (20 mL at each timepoint)		BL0001			BL0002	BL0003	BL0004	BL0005
RSV Anti-F IgG ELISA		X			X	X	X	X
RSV MN		X			X	X	X	X
CMI assessments‡ (mL at each timepoint)		WB0001		WB0002				
Whole Blood for TruCulture		X		X				
Biobank Sampling§ (15 mL at each timepoint)		X			X	X	X	X
TOTAL (mL)	**20**	**39**	**-**	**19**	**50**	**35**	**35**	**35**

Abbreviations: BL: blood sample for immunogenicity; BS: blood sample for safety; CMI: cell-mediated immunity; ELISA: enzyme-linked immunosorbent assay; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibodies; HIV: human immunodeficiency virus; IgG: immunoglobulin G; MN: microneutralization; RSV: respiratory syncytial virus; WB: blood sample for TruCulture.

* D04 (V02) does not apply to the Main Cohort
†The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements
‡ Only applicable for a subset of participants at some selected sites
§ Sample will be collected and stored for potential future safety and immunological research

Table 18: Blood sampling volume (mL) per visit – Booster Cohort Phase I/IIa (participants aged 60 years and older)

Visit Number (V) **Trial Timelines (Days [D]/ Months [M])** **Time Windows (Days)**	**Screening V08** **- D14 M12 to - D01 M12**	**V08** **12M** **+14D**	**V09** **V08+7D** **+1D**	**V10** **V08+28D** **+7D**	**V11** **V08+89D** **+14D**	**V12** **V08+179D** **+14D**	**V13** **V08+364D** **+28D**
Screening serology (HIV Ab, HBsAg, HBcAb, HCV Ab) (~5 mL)	X						
Clinical Safety Laboratory (approximately 15 mL at each timepoint)*	BS0001A		BS0002A	BS0003A			
Hematology, Coagulation, Serum Chemistry (see Table 22)	X		X				
Immunogenicity assessments (20 mL at each timepoint)				BL0006	BL0007	BL0008	BL0009
RSV Anti-F IgG ELISA				X	X	X	X
RSV MN				X	X	X	X
Biobank Sampling (15 mL at each timepoint)†				X	X	X	X
TOTAL (mL)	**20**	**0**	**15**	**50**	**30**	**30**	**30**

Abbreviations: BL: blood sample for immunogenicity; BS: blood sample for safety; ELISA: enzyme-linked immunosorbent assay; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibodies; HIV: human immunodeficiency virus; IgG: immunoglobulin G; MN: microneutralization; RSV: respiratory syncytial virus

* The blood volumes of safety laboratories may be adjusted based on local regulations and local laboratories requirements
† Sample will be collected and stored for potential future safety and immunological research

8.1.2.2 Stage 2 (Phase IIa dose-ranging)

Blood samples will be collected as described in the SoA tables (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study Phase IIa dose-ranging, including any extra assessments that may be required, will not exceed 135 mL (see Table 19). The amount of blood collected at each visit will range from 15 mL to 50 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Guidance and information for the sample collection, preparation, storage, and shipment are provided separately.

Table 19: Blood sampling volume (mL) per visit – Phase IIa dose-ranging (participants aged 60 years and older)

Visit Number (V) **Trial Timelines (Days [D] /Months [M])** **Time Windows (Days)**	**Screening** **-D14 to D01**	**V01** **D01**	**V02** **D04** **±1D**	**V03** **D08** **±1D**	**V04** **D29** **+ 7D**
Screening serology (HIV Ab, HBsAg, HBcAb, HCV Ab) (~5 mL)	X				
Clinical Safety Laboratory (approximately 15 mL at each timepoint)*	BS0001		BS0002	BS0003	BS0004†
Hematology, Serum Chemistry (see Table 23)	X		X	X	X
Immunogenicity assessments (20 mL at each timepoint)		BL0001			BL0002
RSV Anti-F IgG ELISA		X			X
RSV Micro-PRNT (A and B strains)		X			X
Biobank Sampling (15 mL at each timepoint)		X			X
TOTAL (mL)	**20**	**35**	**15**	**15**	**50**

Abbreviations: BL: blood sample for immunogenicity; BS: blood sample for safety; ELISA: enzyme-linked immunosorbent assay; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibodies; HIV: human immunodeficiency virus; IgG: immunoglobulin G; MN: microneutralization; RSV: respiratory syncytial virus
* 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.

8.2 Efficacy and Immunogenicity Assessments

Planned time points for all immunogenicity assessments are provided in the SoAs.

8.2.1 Efficacy Assessments

8.2.1.1 Stage 1 (Phase I/IIa)

No clinical efficacy data will be obtained during study Phase I/IIa. However, frequency of RSV-associated illness is an exploratory objective of this Stage. Participants will notify clinical sites if they experience respiratory or systemic symptoms or signs (Table 20) and nasal swab specimens for the detection of RSV and respiratory pathogens (including COVID-19) will be collected from participants with any respiratory disease episodes. See Section 8.2.1.1.1 for further details.

Table 20: Respiratory symptoms and signs, systemic symptoms or signs, and LRTD symptoms and signs

Systemic symptoms or signs	Upper respiratory symptoms or signs	Lower respiratory symptoms	Lower respiratory signs
[redacted]	[redacted]	[redacted]	[redacted]

The following definitions will be used:

Acute Respiratory Disease (ARD):

[redacted]

Medically Attended Acute Respiratory Disease (MAARD):

[redacted]

Lower Respiratory Tract Disease (LRTD):

[redacted]

Severe LRTD due to RSV: An event meeting the case definition of RSV-LRTD plus at least 1 of the following:

[redacted]

Related to the frequency of detected cases by other respiratory pathogens included in the GenMarkDx test, the same definitions are applicable.

8.2.1.1.1 Nasal Swab Collection (Stage 1 only)

Nasal swab specimens for the detection of RSV and respiratory pathogens (including COVID-19) will be collected from participants with any respiratory disease episodes. 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 subject is discharged, if deemed appropriate by the study investigator. All the nasal swab specimens will be collected in the recommended viral transport media tube. 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 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.

8.2.2 Immunogenicity Assessments

Assays will be performed by Sanofi laboratory (Swiftwater, PA, US) or by an external testing laboratory under Sanofi Pasteur laboratory responsibility.

8.2.2.1 RSV PRNT (micro-PRNT)

[redacted]

8.2.2.2 RSV Anti-F IgG ECL

[redacted]

8.2.2.3 Cell-Mediated Immunity (Stage 1 only)

The T helper cell response will be assessed by using fresh whole blood (TruCulture).

[redacted]

8.2.3 GenMarkDx RP2 PCR

Testing of nasal swab specimens for the detection of RSV and respiratory pathogens (including COVID-19) will use a multiplex polymerase chain reaction (PCR) (GenMarkDx RP2). The GenMarkDx RP2 test can detect the following pathogens: adenovirus, coronavirus (229E, KHU1, NL63, OC43), SARS-CoV-2, hMPV, human Rhino/Enterovirus, Influenza A, Influenza A H1, Influenza A H1-2009, Influenza A H3, Influenza B, PIV1, PIV2, PIV3, PIV4, RSV A, RSV B,

Chlamydia pneumoniae, and *Mycoplasma pneumoniae*. GenMarkDx PCR is a commercial test and validation will be completed either at the Sanofi laboratory or at a clinical research organization under Sanofi's guidance.

8.2.4 Exploratory Objectives-Related Assays

[redacted]

8.3 Safety Assessments

This section presents safety assessments other than AEs, which are presented in Section 8.4.

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

8.3.1 Physical Examinations

At the Screening visit (Stage 1 [Phase I/IIa] and Stage 2 [Phase IIa dose-ranging stage]), the investigator or a designee will perform a full physical examination. A full physical examination will also be completed at Visit 01.

Targeted physical exams will be completed for all subsequent in-person visits at timepoints specified in the SoAs (Section 1.3).

Information will be recorded in the source document.

8.3.2 Vital Signs

Oral (preferred) or axillary pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.3.3 Electrocardiograms

An ECG will be performed at the screening visit to serve as a baseline and to exclude participants with probable or possible myocarditis, pericarditis, and/or myopericarditis, as well as to identify participants with clinically relevant abnormalities that may affect participant safety or study results. In the event a participant develops signs or symptoms suggestive of myocarditis, pericarditis, and/or myopericarditis during the conduct of the study, additional ECG(s) will be performed as rapidly as possible, at an unscheduled visit, if necessary.

The ECG will be available in the source document. Any assessment will be based on standard medical care.

8.3.4 Clinical Safety Laboratory Assessments

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and the SoAs (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring after either the primary or the booster vaccination as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal after either the primary or the booster vaccination should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or RMO.
    - If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 10.2, must be conducted in accordance with the SoA (Section 1.3) and the laboratory manual.
    - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded.

8.3.5 Pregnancy Testing

For the Sentinel Cohort (Phase I/IIa), urine or serum pregnancy testing will be performed in women of childbearing potential before vaccination.

8.4 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

For Phase I/IIa, solicited injection site reactions and solicited systemic reactions will be collected from the day of vaccination (D01 for Sentinel and Main Cohorts; 12 months post-primary vaccination for the Booster Cohort) until 7 days after vaccination (V01/D01+ 7 days for Sentinel and Main Cohorts; V08 + 7 days for the Booster Cohort).

For Phase IIa dose-ranging stage, solicited injection site and systemic reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (V01/D01 + 7 days).

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards and CRF, together with the intensity scales, are presented in Appendix 10.3.5.2.

Unsolicited Non-serious Adverse Events

For Phase I/IIa, unsolicited non-serious AEs will be collected from the day of IMP vaccination (D01 for Sentinel and Main Cohorts; 12 months post-primary vaccination for the Booster Cohort) until 28 days after vaccination (D01+ 28 days for Sentinel and Main Cohorts; V08 + 28 days for the Booster Cohort).

For Phase IIa dose-ranging stage, unsolicited non-serious AEs will be collected from the day of vaccination (D01) until 28 days after vaccination.

The intensity grading scale for unsolicited non-serious AEs is presented in Appendix 10.3.5.3.

Medically Attended Adverse Events (MAAEs)

For Phase I/IIa, MAAEs will be collected from the day of vaccination (D01) until 28 days after vaccination (D01+ 28 days for Sentinel and Main Cohorts; V08 + 28 days for the Booster Cohort).

For Phase IIa dose-ranging stage, MAAEs will be collected throughout the study.

Adverse Events of Special Interest (AESIs)

For Phase I/IIa (Stage 1) and Phase IIa dose-ranging (Stage 2), AESIs will be collected throughout the study.

See Section 8.4.6 for the list of AESIs.

SAEs

Phase I/IIa

Information on SAEs will be collected and assessed throughout the study from the time of the vaccination until 12 months after vaccination for the Sentinel and Main Cohorts. SAEs will be

collected and assessed from the time of the booster vaccination until 12 months after the booster vaccination for the Booster Cohort. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF (eg, SAEs related to blood sampling or study procedure performed during a screening visit).

Phase IIa dose-ranging

For Phase IIa dose-ranging, SAEs will be collected and assessed throughout the study from the time of the vaccination until 6 months after vaccination.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These diary cards will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants to collect the information recorded in the diary card and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the investigator or designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant refuses further contact. All AEs that are considered by the investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.4.6), will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs and Other Safety Reporting

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and/or other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Pregnant women are not eligible to participate in the study and women of childbearing potential in the Sentinel Cohort of **Stage 1 (Phase I/IIa)** agree to use an effective contraceptive method, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery; this information will be collected in the Sponsor Global Pharmacovigilance database. Pregnancies with an estimated conception date up to 12 weeks after study vaccination are to be reported throughout the study.
- If a pregnancy is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 months beyond the estimated delivery date, but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4.

While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention until delivery or until delivery and end of lactation. However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

8.4.6 Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate.

AESIs will include:

- Anaphylactic reactions (including bronchospasms and laryngeal spasms)
- Myocarditis, pericarditis, and myopericarditis

For each AESI, standard case definitions will be used for analysis and presentation of cases: the CDC's case definitions for myocarditis, pericarditis, or myopericarditis (40), and the Brighton Collaboration case definitions for Anaphylaxis (41).

Acute chest pain, shortness of breath, palpitations, or other signs or symptoms potentially compatible with myocarditis or pericarditis (even if not meeting myocarditis/pericarditis CDC case definition), occurring up to 6 weeks after vaccination should be reported as AESI as soon as myocarditis or pericarditis is not clearly ruled out. Participants reporting signs or symptoms suggestive of myocarditis or pericarditis will be referred to a cardiologist or visit to the Emergency Department for evaluation and management, as applicable.

The CDC's definitions of myocarditis, pericarditis, and myopericarditis are provided in Appendix 10.3.6. A Cardiac Adjudication Committee will also evaluate such cases.

Cases adjudicated as meeting the definition of myocarditis or pericarditis by the Cardiac Adjudication Committee will be considered as serious and followed until resolution of symptoms and abnormal test findings. Any AESI reported as related by the investigator will be evaluated by the SMT without delay.

8.4.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.3.1 for definition of MAAEs.

8.4.8 Medication Errors, Misuses or Abuses of Medicinal Product

Definitions of medication error, misuse or abuse can be found in Appendix 10.5.

Since the study interventions are administered by a health care professional, misuse and abuse are not applicable in this study.

8.4.9 Early Safety Data Review

8.4.9.1 Stage 1 (Phase I/IIa)

In Stage 1 (Phase I/IIa), ESDRs were performed for each of the 3 dose-levels in the Sentinel Cohort, the goal of which was to allow for a cautious, stepwise approach to vaccine dose- escalation, and to assure that all participants were safe after 7 days of vaccination. The enrollment of participants and dose-escalation in the study was based on the favorable safety reviews by an internal, unblinded SMT. Safety reviews completed in each ESDR by the SMT included an assessment of the following safety parameters: immediate unsolicited non-serious AEs, solicited injection site and systemic reactions, biological safety laboratory abnormalities, unsolicited AEs reported as related by the investigator, MAAEs, AESIs, and SAEs. Enrollment was paused before each dose-level escalation during the Sentinel Cohort. Enrollment in each subsequent group in the Sentinel Cohort could proceed if investigations by the SMT concluded that there was no unreasonable and significant risk for study participants.

- The first ESDR started with the Sentinel Cohort Low Dose-Level. This safety review was planned when a minimum of 20 participants were vaccinated on D01 and had safety data for 7 days post-vaccination (D01-D08).
- The second ESDR occurred when a minimum of 20 participants in the Sentinel Cohort Medium Dose-Level were vaccinated on D01 and had safety data for 7 days post vaccination (D01-D08). This ESDR also included an assessment of cumulative safety data from the participants in the Sentinel Cohort Low Dose-Level.
- The third ESDR occurred when a minimum of 20 participants in the Sentinel Cohort High Dose-Level were vaccinated on Day 01 and had safety data for 7 days post-vaccination (D01-D08). This ESDR consisted of a cumulative review of the safety data available from the Sentinel Cohort Low Dose-Level and Sentinel Cohort Medium Dose-Level prior to enrolling participants in the Main Cohort. The SMT could also consider data external to the study to decide on progression between Sentinel and Main Cohort stages (eg, based on data generated with similar products in other studies).

At the time of this Amendment, enrollment and planned safety assessments for the Main Cohort have been completed, with no safety issues identified.

8.4.9.2 Stage 2 (Phase IIa dose-ranging)

In Stage 2 (Phase IIa dose-ranging), multiple safety analyses will be performed, minimally at D07 and D28. Additional analyses may be performed as data are available.

8.4.10 Safety Surveillance

Continuous monitoring of participants' safety and signal detection at any time during the study will be performed by the Sponsor's internal Safety Management Committee (see Section 10.1.5).

Safety surveillance by the SMT includes:

- Early Safety Data Reviews (during enrollment of Sentinel Cohort; see Section 8.4.9)
- Periodic Safety Management Team review with frequency adapted to the recruitment phase

- Urgent ad hoc SMT review (as needed, at any time of the study): for each related SAE and AESI case within 1 business day of receipt

The SMT is empowered to recommend a pause in both recruitment and/or further vaccination while it investigates any potential signal or concern. Any safety issues resulting from reviews by the SMT (ESDR, periodic SMT, or ad hoc SMT), will be escalated for review at a PSB (internal, independent, senior safety review committee) in a timely manner.

For Stage 1 (Phase I/IIa), an internal Sponsor Safety Evaluation Review Team (SERT) independent of the study team will review safety data in an unblinded manner if recommended by the PSB.

8.4.10.1 Alert Thresholds for Stage 1 (Phase I/IIa Sentinel Cohort)

If any of the following alert thresholds are met during the Sentinel Cohort, a decision based on the SMT recommendation will be made as to whether or not further enrollment in the corresponding Main Cohort study group will progress, and also as to whether or not dose-escalation (if applicable) for the next Sentinel Cohort can be triggered (at ESDR steps), or whether any modification of the study is needed:

- Any participant who develops an SAE assessed as being of possible, probable, or certain causality
- Two participants report Grade 3 fever without concurrent infectious disease
- Two participants report Grade 3 injection site reactions
- Two participants develop the same or similar Grade 3 or higher AE assessed as being of possible, probable, or certain causality

8.4.10.2 Alert Thresholds for Stage 2 (Phase IIa dose-ranging)

If any of the following alert thresholds are identified from ongoing surveillance, the SMT will review the data in timely manner (within 1 business day, if possible) and escalate the conclusion and recommendation to the PSB chairs and co-chairs or delegates who will decide whether to pause the recruitment:

- ≥ 10% (not less than) o f subjects having the same solicited injection site reactions of ≥ Grade 3
- ≥ 10% (not less than) o f subjects having the same solicited systemic reactions of ≥ Grade 3
- > 2 participants having the same laboratory test (eg, creatinine) with an abnormality (results abnormal per local range) of ≥ Grade 3 that cannot be explained by underlying disease
- > 2 participants having the same or similar unsolicited reaction of ≥ Grade 3 assessed as related to the study vaccine by the investigator

Case unblinding may be performed for above reviews if necessary.

8.4.10.3 Pausing Rules

8.4.10.3.1 Pausing Rules for Stage 1 (Phase I/IIa) Sentinel and Main Cohorts

For the Phase I/IIa Sentinel and Main Cohorts, data will be reviewed by the Sponsor for identification of the following events observed across treatment groups that would potentially contribute to a requirement to pause the study during the recruitment period.

- Any participant develops a vaccine-related life-threatening or fatal SAE, assessed as being of possible, probable, or certain causality by both the investigator and the Sponsor
- One participant develops laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention
- One participant develops a vaccine-related SAE assessed as being of possible, probable, or certain causality
- One participant develops myocarditis, pericarditis, and/or myopericarditis (per CDC definitions listed in Appendix 10.3.6) adjudicated by a Cardiac Adjudication Committee and assessed as related to the study vaccine by the investigator and the Sponsor
- Two participants develop solicited injection site reactions of ≥ Grade 3
- Two participants develop solicited systemic reactions of ≥ Grade 3
- Two participants have the same laboratory test (eg, creatinine) with an abnormality of ≥ Grade 3 that cannot be explained by underlying disease
- Two participants develop the same or similar Grade 3 or higher AE assessed as being of possible, probable, or certain causality
- Any AE which, in the opinion of the investigator and the Sponsor, indicates that human participants would be exposed to an unreasonable and significant risk of illness or injury

If any of the above criteria are met, a decision will be made based on the cumulative safety data assessed by the SMT to decide whether enrollment in the study will be allowed to resume or any study modifications are needed.

Case unblinding may be performed for above reviews if necessary.

8.4.10.3.2 Pausing Rules for Stage 1 (Phase I/IIa) Booster Cohort

For the Phase I/IIa Booster Cohort, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause the study during the recruitment period:

- Any participant develops a vaccine-related SAE, assessed as related to the study vaccine by the investigator
- Any AE which, in the opinion of the investigator and the Sponsor, indicates that human participants would be exposed to an unreasonable and significant risk of illness or injury
- Any participant develops myocarditis, pericarditis, and/or myopericarditis (as adjudicated by an external cardiac adjudication committee), assessed as related to the study vaccine by the investigator
- Any participant develops laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention

If any of the above criteria are met, a decision will be made based on the cumulative safety data assessed by the SMT to decide whether enrollment in the study will be allowed to resume or any study modifications are needed.

8.4.10.3.3 Pausing Rules for Stage 2 (Phase IIa dose-ranging)

For the study Stage 2 (Phase IIa dose-ranging), data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause the study during the recruitment period.

- Any participant develops a vaccine-related SAE, assessed as related to the study vaccine by the investigator
- Any participant develops myocarditis, pericarditis, and/or myopericarditis (as adjudicated by an external cardiac adjudication committee), assessed as related to the study vaccine by the investigator
- Any participant develops laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention
- Any AE which, in the opinion of the investigator and the Sponsor, indicates that human participants would be exposed to an unreasonable and significant risk of illness or injury

If any of the above criteria are met, a decision will be made based on the cumulative safety data assessed by the SMT to decide whether enrollment in the study will be allowed to resume or any study modifications are needed.

Case unblinding may be performed for above reviews if necessary.

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.2.2) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.2.2.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11 Leftover Biological Samples

Any unused part of the biological samples collected for this study (ie, blood samples for safety and immunogenicity, nasal swabs) are being retained in long-term storage (for up to 25 years after

the end of the study) to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. The biological samples will be securely stored at the Sanofi Pasteur laboratory. Relating data will be stored for up to 25 years.

The other biological samples collected to qualify the participants for inclusion in the study or to monitor their health during the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

8.12 Use of Data for Future Research

Future research may help further the understanding of disease and the development of new vaccines/medicines. Reuse of coded data and biological samples (leftover) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study intervention to the Sponsor or which is co-developing the study intervention with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Any unused part of the biological samples collected for this study (ie, blood samples for safety and immunogenicity, nasal swabs) are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local informed consent form [ICF]). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

Data protection – Processing of coded clinical data

The study participants will be provided with all mandatory details of the data processing in the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Study participant data for future research will be stored for up to 25 years after the end of the study.

Use of leftover samples for future research

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol.

The study participants will be provided with all mandatory details of the use of the human biological samples (leftover) in the ICF.

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study.

Any samples remaining at the end of the retention period will be destroyed. If participants request destruction of their samples before the end of the retention period, the investigator must notify the

Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 Statistical Considerations

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

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

9.2 Analysis Sets

9.2.1 Stage 1 (Phase I/IIa)

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

Participant Analysis Set	Description
Screened Participants with - CRF	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. 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 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]
Subpopulation for exploratory objectives	A subset of FAS1 will be used for CMI analyses (FAS1 CMI); details will be provided in the Statistical Analysis Plan (SAP) 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

9.2.2 Stage 2 (Phase IIa dose-ranging)

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

Participant Analysis Set	Description
Screened Participants	All screened 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]

9.3 Statistical Analyses

9.3.1 General Considerations: Stage 1 (Phase I/IIa) and Stage 2 (Phase IIa dose-ranging)

9.3.1.1 General Considerations

All analyses will be descriptive. Key statistics are presented in Table 21. Details will be provided in the SAP.

Table 21: Key view on descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number and percentage of participants
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum
Safety results	**Categorical data**	Solicited and biological safety: Number and percentage (95% CIs) of participants Unsolicited: Number and percentage (95% CIs) of participants, and number of events
	Continuous data	At least mean, standard deviation, minimum, and maximum
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of participants
	Continuous data (titer/data)	Log_{10}: Mean and standard deviation Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum Graphical representation by reverse cumulative distribution curve (RCDC)
Exploratory objectives	**Continuous/Categorical data**	To be determined at the time of the SAP / exploratory SAP

Safety analyses will be performed on the SafAS. Immunogenicity analyses will be performed on the appropriate PPAS and FAS.

9.3.2 Stage 1 (Phase I/IIa)

9.3.2.1 Primary Analysis

9.3.2.1.1 Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, AESIs, MAAEs and SAEs will be described by study group with the 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions.

In addition, biological safety will be analyzed, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) and according to severity grades.

For Phase I/IIa, the main safety parameters will also be described by LNP (all dose-levels pooled).

9.3.2.1.2 Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs. The 95% CIs for the geometric mean titers (GMTs) and GMT ratios (GMTRs) will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

RCDCs will be performed for baseline (D01) and at different timepoints post-vaccination.

Additionally, the effect of dose level on the immune response may be explored through linear model for log post-vaccination titers, including dose level and LNP as an independent factor. More details will be provided in the SAP.

9.3.2.2 Secondary Endpoints Analysis

9.3.2.2.1 Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, AESIs, MAAEs and SAEs will be described by study group with the 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions.

9.3.2.2.2 Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs at each timepoint. The 95% CIs for GMTs and GMTRs will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

9.3.2.2.3 Exploratory Endpoints Analysis

The analysis plan will be described in the SAP or in a separate exploratory SAP. The analyses will contribute to address mechanisms of action questions.

9.3.3 Stage 2 (Phase IIa dose-ranging)

9.3.3.1 Primary Endpoint Analysis

9.3.3.1.1 Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, AESIs, MAAEs, and SAEs will be described by study group with the 95% CIs of

point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions.

In addition, biological safety will be analyzed, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) and according to severity grades.

9.3.3.1.2 Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs at each timepoint. The 95% CIs for GMTs and GMTRs will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

9.4 Sequence of Analyses

9.4.1 Stage 1 (Phase I/IIa)

For Phase I/IIa, there was an ESDR after each dose group in the Sentinel Cohort to determine whether the next group will be enrolled. This ESDR was performed in an unblinded manner by the SMT with a goal of allowing a cautious stepwise approach to vaccine administration.

A first interim statistical analysis of all safety data collected up to D29 and immunogenicity data obtained at D01 and D29 was conducted once data were available on all participants from the Sentinel Cohort. [redacted]

A second interim statistical analysis of all safety data collected up to D29 and immunogenicity data obtained at D01 and D29 was conducted sequentially until all data were available on all participants from the Main Cohort. [redacted]

A third interim statistical analysis of all safety data and immunogenicity data collected up to Month 12 will be conducted once data are available on all participants from the Main Cohort.

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.

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

The SAP will describe the planned interim analyses in greater detail.

9.4.2 Stage 2 (Phase IIa dose-ranging)

In Stage 2, multiple safety analyses will be performed, minimally at D07 and D28. Additional analyses may be performed as data are available. Further details will be provided in the SAP.

9.5 Sample Size Determination

9.5.1 Stage 1 (Phase I/IIa)

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. [redacted]

9.5.2 Stage 2 (Phase IIa dose-ranging)

[redacted]

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements. Similarly, "legally acceptable representative" is used in the protocol whereas "guardian" is used in the C F.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other laws and regulations as applicable, eg:
    - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use
    - 21 CFR
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being

performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity
- The participant in a clinical study has the right to opt out of being notified by the investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, investigators should seek independent ethical advice before determining next steps
- In case the participant has decided to opt out, the investigator must record in the site medical files that she/he does not want to know about such findings

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and if applicable, 21 CFR, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EAA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

The Sponsor shall ensure that all parties involved in the conduct of the clinical study promptly report any events that might meet the definition of a serious breach.

Therefore, investigators shall, within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal investigator must have a process in place to ensure that the site staff or service providers engaged by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the investigator's contract.

10.1.3 Informed Consent Process

- The ICF will be provided to the study participant in paper version.
- The investigator or the investigator's representative will explain the nature of the study, including the potential risks and benefits, to the participants and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The presence of 1 or more witnesses is required for all participants, in accordance with local regulations.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study. Where participants are not in the study anymore, the Sponsor must define if those participants must or not reconsent or be informed of the revision (eg, if the processing of personal data is modified, if the Sponsor changes).
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the 7-day window of the Screening visit from the previous ICF signature date; all participants are required to sign a new ICF outside of this window.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research, unless prohibited by local laws or IRBs/IECs. The investigator or designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Before the start of the study, the investigator or sub-investigator will contact an appropriate pool of potential participants and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to the Sponsor prior to submission to the IRB/IEC for approval.

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participants' race and ethnicity will be collected in this study because these data are required by regulatory agencies.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participants as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of participants concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The

institution and/or investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "product development program", ie, for this study as well as for the following steps necessary for the development of the investigational product including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
- Personnel within Sanofi or partners or service providers involved in the study
- Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
- The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
- Sanofi's Binding Corporate ul es for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 46 Avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

Participant safety will be continuously monitored by the Sponsor's internal safety review committee, which includes safety signal detection at any time during the study. The Sponsor's internal safety review committee, led by the PV representative and the RMO, will be responsible for the review, assessment, and evaluation of safety data generated from this study. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

In the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis, cardiac monitoring data will be assessed by an external Cardiac Adjudication Committee.

Internal Committees

- Participant safety will be monitored by the Sponsor's internal SMT. The SMT, consisting of clinical and pharmacovigilance members of the study team, will be responsible for the blinded review (unblinded review only during Sentinel Cohort), assessment, and evaluation of safety data generated from this study. Core SMT members include Global Safety Officer (lead), Pharmacovigilance Scientist (coordinator), Clinical Development Physician and Statistician. This committee is empowered to recommend a pause in recruitment and/or further vaccination at any time while it investigates any potential signal or concern. The goal is to optimize risk management activities and better assess the benefit/risk profile of the investigational vaccine. For example, when a protocol-predefined pausing rule is identified, the SMT reviews the data and makes the recommendation whether to extend the pause or resume the study.

- Product Safety Board (PSB) will review any safety issues escalated by SMT and all relevant safety and effectiveness data, which may impact the benefit/risk profile of the product. The PSB is an internal, cross-functional, senior safety committee, independent from the study team. The PSB is chaired by the Vaccine GBU Global Medical Head and co-chaired by GBU Pharmacovigilance Head ; GBU Clinical Sciences Head, Research and Development. This committee is empowered to recommend to pause or terminate the study.
- For Phase I/IIa (Stage 1), an internal Sponsor Safety Evaluation Review Team (SERT) independent of the study, will review safety data in an unblinded manner if recommended by PSB. The SE T i s an internal team of the Sponsor's organization that maintains appropriate firewalls with the project team. The SERT includes members of clinical and safety expertise who are not part of the study project team to guarantee independence of the assessment, and includes at least a GSO, CDP, and statistician.

External Committees

- In the event a participant develops symptoms of myocarditis, pericarditis, and/or myopericarditis, cardiac monitoring data will be assessed by an external Cardiac Adjudication Committee using standard case definitions to ensure standardized adjudication of cases.

10.1.6 Dissemination of Clinical Study Data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on

Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations."

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion instructions
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systemic issues that can impact participant safety and or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- The protocol will be signed by the RMO, and a Protocol Investigator Agreement Form (PIAF) will be signed by all investigators. The clinical study report will be signed by the RMO and the coordinating investigator. In case no coordinating investigator has been designated, it will be the responsibility of the RMO or designee(s) to identify the signatory investigator.

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Study personnel will be informed on which clinical supplies will be provided by the Sponsor or the site.

The study start date is considered the date of the first visit planned in the SoAs of the first participant.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study site has all the documents necessary for archiving and a study site closure visit has been performed along with a Site Close Out Form submitted to the IRB, as required.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the investigator's contract.

10.2 Appendix: Clinical Laboratory Tests

- The tests detailed in Table 22 and Table 23 will be performed by the local laboratory.
- Local laboratory results must be recorded in source documents and CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- At Screening and at V03 (Sentinel and Main Cohorts) or V09 (Booster Cohort) of the Phase I/IIa stage, and V02 of the Phase IIa dose-ranging stage, a serum volume sample will be taken for Troponin I level testing as part of the safety laboratory assessments. Other Troponin I samples, as detailed in the SoAs, will be stored for potential future testing of Troponin I level in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis (Screening blood sample will be used as baseline). See also Appendix 10.3.6.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 22: Protocol-required safety laboratory tests (Stage 1, Phase I/IIa only)

Laboratory assessments	Time period for assessment	Parameters
Hematology	Screening V02 (D04; Sentinel Cohort only) V03 (D08) V04 (D29) V09 (7d after booster vaccination; Booster Cohort only) V10 (28d after booster vaccination, Booster Cohort only)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Eosinophils Hemoglobin Platelet count Red blood cell (RBC) count
Clinical Chemistry	Screening V02 (D04; Sentinel Cohort only) V03 (D08) V04 (D29) V09 (7d after booster vaccination; Booster Cohort only) V10 (28d after booster vaccination, Booster Cohort only)	Blood urea nitrogen (BUN) Creatinine Glucose (random) Potassium Sodium Calcium Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Alkaline phosphatase Total bilirubin Direct bilirubin Total protein Troponin I
Coagulation parameters	Screening V02 (D04; Sentinel Cohort only) V03 (D08) V04 (D29) V09 (7d after booster vaccination; Booster Cohort only) V10 (28d after booster vaccination, Booster Cohort only)	Prothrombin time Activated partial thromboplastin time (APTT)
Other Screening Tests	Screening	HIV antigen/antibody test Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody Urine or serum pregnancy test (V01) for Sentinel Cohort

Note 1: -In case of abnormal safety laboratory results, unscheduled visits or additional laboratory assessments or procedures may occur based on investigator's judgment to ensure the participant's safety.

Note 2: Once it has been determined that no additional testing for Troponin I or other safety parameters is needed, biobank blood samples may be subject to any current or future use as per the protocol.

Table 23: Protocol-required safety laboratory tests (Stage 2, Phase IIa dose-ranging)

Laboratory assessments	Time period for assessment	Parameters
Hematology	Screening V02 (D04) V03 (D08)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Eosinophils Basophils Monocytes Hemoglobin Platelet count
Clinical Chemistry	Screening V02 (D04) V03 (D08)	Creatinine Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Alkaline phosphatase Total bilirubin C-reactive protein
	Screening V02 (D04)	Troponin I
Other Screening Tests	Screening	HIV antigen/antibody test Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody

Note 1: -In case of abnormal safety laboratory results, unscheduled visits or additional laboratory assessments or procedures may occur based on investigator's judgment to ensure the participant's safety.

Note 2: Once it has been determined that no additional testing for Troponin I or other safety parameters is needed, biobank blood samples may be subject to any current or future use as per the protocol.

Investigators must document their review of each laboratory safety report.

10.3 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination/booster administration and the next 7 days).

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: “Administration site reaction” term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

Systemic ARs are all ARs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

Medically Attended AE (MAAE)

An MAAE is a new-onset or a worsening of a condition that prompts the participant to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. hen in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is other medically important event • The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment. Medical or scientific judgment should be exercised by the investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the IMP injection site (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the IMP (see definition in Section 6) and therefore are referred to as reactions and do not require the investigator's opinion on relatedness.

Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:

- For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the investigator only.
- For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the investigator and the Sponsor (except for injection site reactions which will be related by default). Sponsor assessment is entered in the GPV database only.
- For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.

The investigator is obliged to assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:

  - Not related – The AE is clearly / most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)
  - Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causal relationship assessment, the investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- The investigator must review and provide an assessment of causal relationship for each unsolicited AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Serious AEs likely to be related to the study intervention, that persist at the end of the study will be followed up by the investigator until their complete disappearance or the stabilization of the participant's condition. The investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor via Paper CRF

The SAE paper CRF can be sent to the Sponsor by one of the following means:

- By fax, to the following number: +33 160 497 070
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com
- By express mail, to the following address:

  Global Pharmacovigilance, Sanofi Pasteur

  Discovery Drive
  Swiftwater, PA 18370

Using a Verbal Autopsy Questionnaire to Aid in Determining the Cause of Death

In case of the absence or inadequacy of health information that would allow a thorough evaluation of the causes of the death of a study participant, the verbal autopsy procedure may be triggered by either the investigator or the Sponsor. Detailed instructions on the use of the verbal autopsy questionnaire, as well as the questionnaire itself, are provided in the Operating Guidelines.

Safety Emergency Call
If, as per the investigator's judgment, a participant experiences a medical emergency, the investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines. This process does not replace the need to report an SAE. The investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department. In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.4.

10.3.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the “FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 00 ” .

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.2 Solicited AR Intensity Grading Scale

10.3.5.2.1 Stage 1 (Phase I/IIa)

Table 24: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged ≥ 12 years (Phase I/IIa)

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:** ≥ to ≤ 50 mm **Grade 2:** ≥ 1 to ≤ 100 mm **Grade 3:** > 100 mm	**Grade 1:** ≥ to ≤ 50 mm **Grade 2:** ≥ 1 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 25: Solicited systemic reactions: terminology, definitions, and intensity scales – children aged 2 through < 12 years, adolescents, or adults (aged ≥ 12 years) (Phase I/IIa)

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	Tiredness	Muscle aches and pains (only new or worsened)	Joint pain (only new or worsened)	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	Fatigue is a new symptom of lack of energy, or tiredness. For participants ≥ 5 years of age, this symptom is the primary complaint, is not relieved by rest and it may interfere with the participant's function.	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

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.

Important notes for the accurate assessment of temperature:

Participants are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The preferred unit for this study is Celsius (Fahrenheit may be used for US sites). The optimal time for measurement is the evening, when body temperature is the highest. Body temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.3.5.2.2 Stage 2 (Phase IIa dose-ranging)

Table 26: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents and adults aged ≥ 12 years (Phase IIa dose-ranging)

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
CRF and DC Intensity scale*	**Grade 1:** No interference with activity **Grade 2:** Repeated use of an over-the-counter (OTC) pain reliever for more than 24 hours or interferes with activity **Grade 3:** Any use of pain reliever that is not OTC and is only obtained by prescription (eg, narcotic) or prevents daily activity	**Grade 1:** ≥ to ≤ 50 mm **Grade 2:** ≥ 1 to ≤ 100 mm **Grade 3:** > 100 mm	**Grade 1:** ≥ to ≤ 50 mm **Grade 2:** ≥ 1 to ≤ 100 mm **Grade 3:** > 100 mm

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.
* For pain, the scale will be provided in the DC and the intensity will be transcribed in the CRF. 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 27: Solicited systemic reactions: terminology, definitions, and intensity scales – children aged 2 through < 12 years, adolescents, or adults (aged ≥ 12 years) (Phase IIa dose-ranging)

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Fatigue	Myalgia (only new or worsened)	Arthralgia (only new or worsened)	Chills
Diary card term	Temperature	Headache	Tiredness	Muscle aches and pains (only new or worsened)	Joint pain (only new or worsened)	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	Fatigue is a new symptom of lack of energy, or tiredness. For participants ≥ 5 years of age, this symptom is the primary complaint, is not relieved by rest and it may interfere with the participant's function.	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	Cold feeling
CRF and DC Intensity scale*	**Grade 1:** ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Fatigue	Myalgia (only new or worsened)	Arthralgia (only new or worsened)	Chills
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	**Grade 2:** Repeated use of an over-the-counter (OTC) pain reliever for more than 24 hours or interferes with activity	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	**Grade 3:** Any use of pain reliever that is not OTC and is only obtained by prescription (eg, narcotic) or prevents daily activity	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity

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.

Important notes for the accurate assessment of temperature:

Participants are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The preferred unit for this study is Celsius (Fahrenheit may be used for US sites). The optimal time for measurement is the evening, when body temperature is the highest. Body temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.3.5.3 Serious and Non-serious Unsolicited AE Intensity Grading Scale

10.3.5.3.1 Stage 1 (Phase I/IIa)

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.2).

All other unsolicited AEs will be classified according to the following intensity scale:

- Grade 1
  - CRF: A type of AE 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.
  - Diary card: No interference with activity.
- Grade 2
  - CRF: A type of AE 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.
  - Diary card: Some interference with activity.
- Grade 3
  - CRF: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - Diary card: Significant; prevents daily activity.

10.3.5.3.2 Stage 2 (Phase IIa dose-ranging)

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.2).

All other unsolicited AEs, including SAEs, will be classified according to the following intensity scale:

- Grade 1: No interference with activity
- Grade 2: Some interference with activity and not requiring therapeutic medical intervention
- Grade 3: Prevents daily activity and requires therapeutic medical intervention

10.3.5.4 Tables for Laboratory Abnormalities

The predefined intensity thresholds for laboratories abnormalities are shown in Table 28 as per the Food and Drug Administration, Center for Biologics Evaluation and Research Guidance for Industry: Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (43). Troponin I values will be interpreted using the local laboratories normal ranges references.

Table 28: Intensity thresholds for laboratories abnormalities

Laboratory Endpoint	Unit	Grade 1	Grade 2	Grade 3
Hemoglobin (Female)	gm/dL	11.0 to 12.0	9.5 to 10.9	≤ .
Hemoglobin (Female) (Change from baseline value)	gm/dL	Any decrease to 1.5	1.6 to 2.0	≥ .1
Hemoglobin (Male)	gm/dL	12.5 to 13.5	10.5 to 12.4	≤ 10.
Hemoglobin (Male) (Change from baseline value)	gm/dL	Any decrease to 1.5	1.6 to 2.0	≥ .1
Increase in WBC	cells/mm3	10 800 to 15 000	15 001 to 20 000	≥ 0 001
Decrease in WBC	cells/mm3	2500 to 3500	1500 to 2499	≤1
Decrease in Absolute Lymphocytes	cells/mm3	750-1000	500 to 749	< 500
Decrease in Absolute Neutrophils	cells/mm3	1500-2000	1000-1499	< 1000
Eosinophils	cells/mm3	650 to 1500	1501 to 5000	> 5000
Decrease in Platelets	cells/mm3	125 000-140 000	100 000 – 124 000	<100 000
PT – increase by factor (prothrombin time)		1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN
PTT – increase by factor (partial thromboplastin time)		1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN
Sodium – Hyponatremia	mEq/L	132 to 134	130 to 131	< 130
Sodium – Hypernatremia	mEq/L	144 to 145	146 to 147	≥ 1 8
Potassium – Hypokalemia	mEq/L	3.5 to 3.6	3.3 to 3.4	< 3.3
Potassium - Hyperkalemia	mEq/L	5.1 to 5.2	5.3 to 5.4	≥ .
Glucose - Random	mg/dL	110 to 125	126 to 200	> 200 or requires insulin or hyperosmolar coma
BUN	mg/dL	23 to 26	27 to 31	> 31 or requires dialysis
Creatinine	mg/dL	1.5 to 1.7	1.8 to 2.0	≥ .1 or requires dialysis
Calcium – Hypocalcemia	mg/dL	8.0 to 8.4	7.5 to 7.9	< 7.5
Calcium – Hypercalcemia	mg/dL	10.5 to 11.0	11.1 to 11.5	> 11.5
Total Protein – Hypoproteinemia	g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0
Alkaline phosphate – increase by factor		1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN
ALT (increase by factor)		1.1 - 2.5 x ULN	2.6 to 5.0 x ULN	≥ 5.1 x ULN
AST (increase by factor)		1.1 to 2.5 x ULN	2.6 to 5.0 x ULN	≥ 5.1 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor		1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN

Source: : Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov) https://www.fda.gov/media/73679/download

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; BUN = blood urea nitrogen; LLN = Lower Limit of Normal; PT = prothrombin time; PTT = partial prothromboplastin time; ULN = Upper Limit of Normal; WBC = white blood cell.

10.3.6 Definitions of Acute Myocarditis, Pericarditis, and Myopericarditis

The CDC's case definitions for myocarditis, pericarditis, or myopericarditis (Table 29) is used for assessment and case presentation. Other identifiable cause of the symptoms and findings should be considered in the assessment.

Table 29: Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms:*	Presence of ≥ 1 new or worsening of the following clinical symptoms:*
	• Chest pain, pressure, or discomfort	• Chest pain, pressure, or discomfort
	• Dyspnea, shortness of breath, or pain with breathing	• Dyspnea, shortness of breath, or pain with breathing
	• Palpitations	• Palpitations
	• Syncope	• Syncope
	OR, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:	*OR*, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:
	• Irritability	• Irritability
	• Vomiting	• Vomiting
	• Poor feeding	• Poor feeding
	• Tachypnea	• Tachypnea
	• Lethargy	• Lethargy
	AND	*AND*
	≥ 1 new finding of	≥ 1 new finding of
	• Troponin level above upper limit of normal (any type of troponin) ‡	• Histopathic confirmation of myocarditis†
	• Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§	
	• Abnormal cardiac function or wall motion abnormalities on echocardiogram	• cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)**
	• cMRI findings consistent with myocarditis**	
	AND	*AND*
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings

Condition	Definition
Acute pericarditis††	Presence of ≥ 2 new or worsening of the following clinical features:
	• Acute chest pain‡‡
	• Pericardial rub on exam
	• New ST-elevation or PR-depression on EKG
	• New or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis

Source: Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-82.
Abbreviations: AV: atrioventricular; cMRI: cardiac magnetic resonance imaging; ECG or EKG: electrocardiogram
* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
† Using the Dallas criteria (Aretz HT, Billingham ME, Edwards D, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3–14). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
‡ For the purpose of this study, Troponin I will be evaluated.
§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
** Using either the original or the revised Lake Louise
criteria. https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon
†† https://academic.oup.com/ei.urheartj/article/36/42/2921/2293375
‡‡ Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

10.4 Appendix: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal
2) Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *F ≥ 1% p wh consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix: Medication Errors, Misuses or Abuses of Medicinal Product

All reports of medication error, misuse or abuse in relation to the IMP with or without an AE must be collected and transmitted to the GPV database following standard processes. The investigator will assess whether or not the medication error, misuse or abuse event has to be reported together with an AE or SAE.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high” (euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

10.6 Appendix: Risk-based Approach

ICH E6- g uideline for GCP is introducing the “risk-based approach” concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.7 Appendix: Protocol Amendment History

The Protocol Amendment Rationale for the current amendment is located directly before the Table of Contents.

11 References

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12 Sponsor Signature Page

Signature Page for VV-CLIN-0625747 v9.0
vae00010-protocol

Approve & eSign	[redacted] Clinical [redacted]