Title Page

Protocol Title:

Immunogenicity and Safety of the First-in-Human SARS-CoV-2 mRNA Vaccine Formulation in Healthy Adults 18 Years of Age and Older

Study Code: VAW00001

Protocol Version Number: 3.0

Amendment Number: 1.0

Compound: SARS-CoV-2 mRNA vaccine: ultra-low-dose (μg), low-dose (μg), or medium-dose (μg)

Study Phase: Phase I/II

Short Title:

Study of mRNA Vaccine Formulation against COVID-19 in Healthy Adults 18 Years of Age and Older

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
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Manufacturer:

Translate Bio
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Regulatory Agency Identifier Number(s):

BB-IND: 26788

WHO UTN: U1111-1251-5486

ClinicalTrials.gov: NCT04798027

Approval Date: 08 April 2021

Medical Monitor Name and Contact Information are provided in the Operating Guidelines.
The study centers, the Investigators at each center, and the Coordinating Investigator are listed in a separate document.

[redacted]

Document History and Protocol Amendment Rationale

Previous Version	Date	Comments
1.0	14 October 2020	Original study design submitted to IRB for review.
2.0	02 February 2021	First version used in the study

IRB: Institutional Review Board

** Version in bold font has been approved by the IEC(s) / IRB(s) and used in the study.*

Overall Rationale for the Amendment:

Background

In the original protocol, the first 15 participants to receive the SARS-CoV-2 mRNA vaccine were to be enrolled in a Safety Sentinel Cohort. These participants were to receive 2 injections of the study intervention, 21 days apart, in an open-label, dose-escalation manner. Five participants were to be enrolled in each of the 3 dose-level groups [redacted]).

As planned in the original protocol, 5 participants were assigned to the low dose-level of [redacted] µg, received their first injection, and were contacted by telephone on Day (D)03 to document local and systemic solicited reactions as well as unsolicited adverse events (AEs). [redacted]

Further considerations of the safety data from the 5 participants assigned to the low-dose level group revealed the transient nature of the reported solicited Grade 3 adverse events. Given the fact that these AEs were self-limited (ie, no subject sought any medical attention) and no major safety concerns were identified, the Sponsor introduced 4 changes through a protocol amendment:

1) add an "ultra-low-dose" arm of [redacted] µg [redacted] to evaluate [redacted] a lower dose-level range (ie, ultra-low- [redacted µg], low- [redacted µg], and medium- [redacted µg] dose-levels); [redacted].
2) increase the number of Sentinel Cohort participants from 5 to 10 in the dose-level groups that have yet to start enrollment (ie, ultra-low- and medium-dose-levels);
3) add an expansion of the open-label Sentinel Cohort for the [redacted] µg dose-level to better understand the reactogenicity at this dose-level in a larger group of participants prior to escalation to the [redacted] µg dose. This possibility to expand the number of Sentinel Cohort participants will also be extended to the ultra-low- and medium-dose groups if needed;
4) decrease the number of placebo recipients in the Full Enrollment Cohort.

[redacted]

Change 1: Introduction of an ultra-low-dose group

[redacted] The introduction of an ultra-low-dose-level group is supported by preclinical immunogenicity data at [redacted] µg dose-level which is provided with the Investigator's Brochure amendment. The initial Sentinel Cohort for this ultra-low-dose will include 10 participants with the option for an Expanded Sentinel Cohort if needed (as described below in Change 3).

Change 2: Increase the number of Sentinel Cohort participants

The number of Sentinel Cohort participants for both the ultra-low- ([redacted] µg) and medium-dose ([redacted] µg) groups will be increased from 5 to 10. This will help make a more comprehensive assessment of the safety and reactogenicity for each of these dose-level groups before study progression.

Change 3: Expansion of the Sentinel Cohort

The Sponsor decided to amend the protocol in order to add an Expanded Sentinel Cohort for the [redacted] µg dose-level and to introduce the option to expand the Safety Sentinel Cohort, if needed, for each of the remaining dose levels. The Expanded Sentinel Cohort for a corresponding dose-level may be triggered only after careful assessment of the Initial Sentinel Cohort for the frequency, severity, and duration of adverse events and proceed if there are no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the vaccine at a given dose-level prior to triggering study progression decisions (within the same dose-level arm, or in relation to progression to other dose-levels). In case an Expanded Sentinel Cohort (15-20 participants) is initiated after the Initial Sentinel Cohort (5-10 participants) for a particular dose level, this will bring the total number of participants for that dose-level group to approximately 25 participants. The Expanded Sentinel Cohort will proceed in a similar manner to the Initial Sentinel Cohort using the same monitoring parameters and safety assessments. The D01-03 safety data for the Expanded Sentinel Cohort participants in that dose-level group will be reviewed by the Sponsor's SMT.

If no safety concern is identified for the [redacted] µg Expanded Sentinel Cohort, then the Initial Sentinel Cohort participants for the [redacted] µg group will be vaccinated. If the Expanded Sentinel Cohort for the [redacted] µg or [redacted] µg dose-level is triggered, the SMT assessment of safety and reactogenicity will help decide if further vaccinations for the corresponding dose-level will proceed.

Change 4: Decrease the number of placebo recipients in the Full Enrollment Cohort

In both age strata (ie, 18-49 years and ≥ 50 years), the number of participants in the placebo arm of the Full Enrollment Cohort has been decreased to half the number of participants in each of the vaccine arm. This will help decreasing the risk of exposing higher number of participants to placebo in the setting of Emergency Use Authorization vaccine rollout and expanding eligibility for vaccines.

Summary

Progression to the Full Enrollment Cohort for all eligible dose-levels will occur following the Complete Sentinel Early Safety Data Review (CS-ESDR) with evaluation of safety data up to D09

[redacted]

post first vaccination in all Sentinel Cohorts participants (ie, in all Initial and triggered Expanded Sentinel Cohorts). The open-label Sentinel Cohort will be followed by a randomized, modified double-blind, placebo-controlled Full Enrollment Cohort to evaluate the safety and immunogenicity of the formulations of the SARS-CoV-2 mRNA vaccine in healthy adult participants (18 years of age and older) in the United States (US) and Honduras.

[redacted]

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Immunogenicity and Safety of the First-in-Human SARS-CoV-2 mRNA Vaccine Formulation in Healthy Adults 18 Years of Age and Older

Short Title:

Study of mRNA Vaccine Formulation Against COVID-19 in Healthy Adults 18 Years of Age and Older

Rationale:

An outbreak of severe respiratory illnesses in Wuhan City, Hubei Province, China in December 2019 heralded the appearance of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the human population. The rapid escalation of the outbreak led to a declaration by the World Health Organization on 20 January 2020 of a Public Health Emergency of International Concern, followed by a declaration on 11 March 2020 of a pandemic (1). As of 2 April 2021, the virus has been detected in 192 countries/regions and infected over 129 million individuals (2). Despite unprecedented measures of isolation, quarantine, social distancing, community containment, use of face covers/masks in public to curb the spread of the virus, and most recently, the emergency use authorization of SARS-CoV-2 vaccines in the US and other locally approved/authorized SARS-CoV-2 vaccines, the global burden of SARS-CoV-2 infections and associated disease continue to grow steadily, highlighting the urgent need for safe and effective vaccines to meet the global need.

The candidate vaccine is developed by Sanofi Pasteur in collaboration with Translate Bio using messenger ribonucleic acid (mRNA) technology and will be manufactured by Translate Bio. The mRNA encodes the full-length spike (S) protein from SARS-CoV-2, with 2 sets of mutations to stabilize the prefusion conformation of the protein. The mRNA is encapsulated within a novel lipid nanoparticle (LNP) vehicle [redacted].

VAW00001 is a first-in-human Phase I/II multi-center study. The original study design comprised 2 sequential cohorts: a lead-in open-label, dose-escalation Sentinel Cohort, followed by a randomized, modified double-blind, dose-ranging, placebo-controlled Full Enrollment Cohort, to evaluate the safety and immunogenicity of the SARS-CoV-2 mRNA vaccine in healthy adult participants (18 years of age and older) in the United States (US) and Honduras. The study was to evaluate both 1 injection (Cohort 1) and 2 injections, given 21 days apart (Sentinel Cohort and Cohort 2) for 3 different dose-levels [redacted] of the candidate mRNA vaccine with the goal of selecting the optimal dose and schedule to proceed to a Phase III study.

[redacted]

[redacted]

After careful assessment of the safety data from the 5 participants assigned to the low-dose level group for the frequency, severity, and duration of adverse events, the Sponsor decided to amend the study protocol. This protocol amendment adds an "ultra-low-dose" arm of [redacted] µg [redacted] It also increases the number of Sentinel Cohort participants in both the ultra-low- ([redacted] µg) and medium-dose ([redacted] µg) groups from 5 to 10. Lastly, it introduces the possibility to expand any of the 3 dose-level groups of the Sentinel Cohort to further assess the D01-D03 safety data of the corresponding dose-level group. This option will be exercised for the low-dose group and remains as a possibility for the ultra-low- and medium-dose groups. With addition of an Expanded Sentinel Cohort, the Sentinel Cohort for each dose-level group could potentially include a total of approximately 25 participants.

The longer-term objective remains to longitudinally define the safety and durability of the immune response induced by the SARS-CoV-2 mRNA vaccine over the 1-year study duration.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Safety To describe the safety profile of all participants in each age group and each study intervention group up to 12 months post-last dose.	***Safety*** • Presence of unsolicited systemic adverse events (AEs) reported in the 30 minutes after each injection • Presence of solicited injection site reactions and systemic reactions (pre-listed in the participant's Diary Card [DC] and Case Report Form [CRF]) occurring up to 7 days after each injection • Presence of unsolicited AEs reported up to 21 days after each injection • Presence of medically attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study • Presence of out-of-range biological test results up to 8 days post-last dose (ie, up to Day [D] 09 for Cohort 1 and up to D30 for Sentinel Cohort and Cohort 2)

[redacted]

Objectives	Endpoints
Immunogenicity To describe the neutralizing antibody profile at D01, D22, and D36 of each study intervention group.	***Immunogenicity*** Neutralizing antibody titers against the SARS-CoV-2 D614G variant will be measured with the neutralization assay • Antibody titer at D01, D22, and D36 • Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36 • 2-fold and 4-fold-rise in serum neutralization titer (post/pre) relative to D01 at D22, and D36 • Occurrence of neutralizing antibody seroconversion defined as baseline values below lower limit of quantification (LLOQ) with detectable neutralization titer above assay LLOQ at D22 and D36
Secondary	
Immunogenicity 1) To describe binding antibody profile at D01, D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) of each study intervention group. 2) To describe the neutralizing antibody profile at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) of each study intervention group.	***Immunogenicity*** Binding antibody titers to trimerized SARS-CoV-2 S protein will be measured for each study intervention group with the enzyme-linked immunosorbent assay method • Individual anti-S antibody concentration at D01, D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Individual anti-S antibody concentration ratio (fold-rise in serum ELISA concentration post-vaccination relative to D01) at D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Fold-rise in anti-S antibody concentration (post/pre) ≥ 2 and ≥ 4 at D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2)

[redacted]

Objectives	Endpoints
	Neutralizing antibody titers against the SARS-CoV-2 D614G variant will be measured with the neutralization assay • Antibody titer at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Fold-rise (fold-rise in serum neutralization titer post-vaccination relative to D01) at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • 2-fold and 4-fold-rise in serum neutralization titer (post/pre) relative to D01 at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2 D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Occurrence of neutralizing antibody seroconversion, defined as values below LLOQ at baseline with detectable neutralization titer above assay LLOQ at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2)
Efficacy 1) To describe the occurrence of virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection. 2) To evaluate the correlation/association between antibody responses to SARS-CoV-2 mRNA vaccine and the risk of virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection.	***Efficacy*** • Virologically-confirmed COVID-19-like illness as defined by specified clinical symptoms and signs and confirmed by a positive result for SARS-CoV-2 nucleic acid viral detection assay • Serologically-confirmed SARS-CoV-2 infection as defined by SARS-CoV-2 Nucleoprotein specific antibody detection immunoassay • Correlates of risk/protection based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization or ELISA, considering virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection as defined above

[redacted]

Overall Design

Type of design	Phase I/II, first-in-human, multi-center, safety and immunogenicity study comprised of 2 sequential cohorts: • Lead-in, open-label, Sentinel Cohort (initial target of 25 participants), with Complete Sentinel Early Safety Data Reviews (CS-ESDRs) In case an alert threshold is met in a dose-level group, the Sentinel Cohort for the corresponding dose-level group could be expanded to reach a total of approximately 25 participants • Randomized, modified double-blind, placebo-controlled Full Enrollment Cohort (initial target of 308 participants, but actual number could be lower as it will be determined by dose-levels progressing after CS-ESDR). Includes Cohort 1 and Cohort 2.
Phase	I/II
Control method	• Open-label, without placebo group for Sentinel Cohort • Placebo-controlled for Full Enrollment Cohort
Study population	Healthy, adults 18 years of age and older without prior serologic evidence of SARS-CoV-2 infection
Countries	United States, Honduras
Level and method of blinding	*For Sentinel Cohort* • Open-label without blinding of participants, site Investigators and staff, and Sponsor • No blinding for injection schedule as all participants will receive 2 vaccinations *For Full Enrollment Cohort* • Blinding for study intervention assignment (formulation): participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff • No blinding for injection schedule • Only study site staff who prepare and administer the vaccine and are not involved with the safety evaluations will be unblinded to study intervention assignment
Study intervention assignment method	Sentinel Cohort: sequentially assigned study intervention; Full Enrollment Cohort: randomization for study intervention and assigned stratification by age

Disclosure Statement:

This is a sequential group prevention study, stratified into 2 age groups based on age at enrollment: the younger adult age group (18-49 years) and the older adult age group (≥ 50 years). There will be up to 3 arms in the Sentinel Cohort followed by up to 8 arms in the Full Enrollment Cohort. The study will be done in an open-label fashion for the Sentinel Cohort and in a double-blind manner for the Full Enrollment Cohort.

[redacted]

Number of Participants:

The study targets enrollment of approximately 333 participants 18 years of age and older (165 adults 18 through 49 years of age and 168 adults 50 years of age and older), without evidence of previous SARS-CoV-2 infection. This number includes all 25 Initial Sentinel Cohort participants and all 308 Full Enrollment Cohort participants (see Table 1.1 and Table 1.2). However, the actual number of participants enrolled will depend on which dose-level are allowed to be evaluated in the Sentinel Cohort and the Full Enrollment Cohort. The number of participants may be higher if Expanded Sentinel Cohorts are exercised for all 3 dose-levels, and if all dose-levels progress to the Full Enrollment Cohort (maximum number of study participants approximately 383); conversely, the number may be lower if not all the dose-levels are evaluated in the Sentinel Cohort or/and not all the dose-levels progress to the Full Enrollment Cohort.

The study population to be enrolled will be comprised of 2 sequential cohorts: the Sentinel Cohort (initial target of 25 participants [younger adults only]. For each dose-level in the Sentinel Cohort, there is an option to expand the group with the inclusion of an additional 15 or 20 participants, depending on the number of participants initially enrolled in that dose-level group. Hence, the entire Sentinel Cohort could include approximately 75 participants, with approximately 25 participants per each dose-level group. Following the assessment of the Sentinel Cohort, the Full Enrollment Cohort will be initiated (initial target of maximum 308 participants; the actual number will be determined by dose-levels progressing after the first Complete Sentinel ESDR [ie, CS-ESDR-1]).

Intervention Groups and Duration:

The Initial Sentinel Cohort participants will be 18 through 49 years of age and will be assigned to receive 2 injections of the study intervention, 21 days apart, in an open-label manner. Clinical safety laboratory evaluations will be performed at screening and 8 days after each injection. The number of participants to be enrolled in each dose-level group, with and without the possible expansion, are shown below in Table 1.1.

Table 1.1: Planned sample size (Sentinel Cohort; 18 through 49 years)

Cohort	Group	Dose-level*	Initial Sentinel Cohort N	Expanded Sentinel Cohort† N	Total Sentinel Cohort N
Sentinel Cohort: 2 injections	**1**	[redacted] µg	10	15	25
	2	[redacted] µg	5	20	25
	3	[redacted] µg	10	15	25

* Formulation: SARS-CoV-2 mRNA: ultra-low-dose ([redacted] µg); low-dose ([redacted] µg); medium-dose ([redacted] µg).

† The Expanded Sentinel Cohort for a corresponding dose-level may be triggered only after careful assessment of the Initial Sentinel Cohort for the frequency, severity, and duration of adverse events and proceed if there are no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the vaccine at a given dose-level prior to triggering study progression decisions.

[redacted]

The Full Enrollment Cohort includes both Cohort 1 and Cohort 2. Participants in Cohort 1 of the Full Enrollment Cohort (hereafter referred to as Cohort 1) will receive a single injection of study intervention while participants in Cohort 2 of the Full Enrollment Cohort (hereafter referred to as Cohort 2) will receive 2 vaccinations (to be given 21 days apart), of one of the study interventions (ultra-low-dose [µg], low-dose [µg], medium-dose [µg], or placebo) at D01 (VAC1). The Full Enrollment Cohort planned sample size, assuming all dose-levels progress to full enrollment, is shown in Table 1.2.

Table 1.2: Planned sample size (Full Enrollment Cohort)

Cohort	Group	Dose-level*	N		Total
			18-49 years	≥ 50 years	
Cohort 1: 1 injection	**1**	µg	20	24	44
	2	µg	20	24	44
	3	µg	20	24	44
	4	Placebo	10	12	22
Cohort 2: 2 injections	**5**	µg	20	24	44
	6	µg	20	24	44
	7	µg	20	24	44
	8	Placebo	10	12	22

* Formulation: SARS-CoV-2 mRNA: ultra-low-dose (µg); low-dose (µg); medium-dose (µg).

Note: A subset of up to 77 randomly selected participants in Cohort 2 (approximately 50% of participants in each of Groups 5 to 8, under 18-49 years and ≥ 50 years age sub-groups) will be included in an Additional Immunological Tests (AIT) subset.

Sentinel Cohorts

Participants in the Sentinel Cohort will receive the first injection of the study intervention (ultra-low-dose [µg], low-dose [µg], or medium-dose [µg] at D01 (Vaccination [VAC] 1) in a staged fashion. The 5 participants assigned to the µg dose-level received their first vaccination and were contacted by telephone on D03 to document local and systemic solicited reactions as well as unsolicited AEs during this period in the CRF.

- The 5 participants in the low-dose (µg) group continued their participation in the study. Following the review of the D01-D09 safety and reactogenicity data, the SMT decided that administration of the second study intervention 21 days after the first one could proceed as planned in the original protocol.

- As per this protocol amendment, the ultra-low-dose ([redacted] µg) group will be introduced. The 10 participants in this new Sentinel Cohort group will receive their first vaccination and will be contacted by telephone on D03 to document local and systemic solicited reactions as well as unsolicited AEs during this period in the CRF.
- Also, concurrent with the initiation of the [redacted] µg Initial Sentinel Cohort, as per this protocol amendment, the Expanded Sentinel Cohort for the low-dose ([redacted] µg) group will enroll an additional 20 participants to better understand the reactogenicity at this dose-level in a larger group of participants.

The progression of the Initial and possible Expanded Sentinel Cohorts are displayed in Figure 1.1.

The Expanded Sentinel Cohort participants in the [redacted] µg dose-level will be contacted by telephone on D03 post-vaccination to document local and systemic solicited reactions as well as unsolicited AEs during this period. Based on the assessment of alert thresholds and other safety parameters for the [redacted] µg dose Expanded Sentinel Cohort, the SMT will determine whether or not the 10 Initial Sentinel Cohort participants for the medium-dose-level of [redacted] µg will be vaccinated.

In addition, ad hoc SMTs for any Sentinel Cohort group may occur to evaluate D01-D09 additional safety data, including laboratory data as needed, to better understand safety. Such ad hoc SMT evaluations will inform study progression, especially if any Sentinel Cohort groups reach the time of second vaccination before the first Complete Sentinel ESDR (ie, CS-ESDR-1) takes place.

For the [redacted] µg and [redacted] µg dose-level groups, an Expanded Sentinel Cohort may be triggered if an alert threshold (see list of threshold in Section 8.4.1) is met in the context of no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the product at a given dose-level prior to triggering study progression decisions (within the same dose-level arm, or in relation to progression to other dose-levels). In case, the Expanded Sentinel Cohort for the ultra-low-dose is triggered, it may run concurrently with the medium-dose Initial or Expanded Sentinel Cohort groups (Figure 1.5). It is to be noted that, if vaccination in the ultra-low- and medium-dose Sentinel Cohort groups do not run concurrently, the possible triggering of an Expanded Sentinel Cohort for the ultra-low-dose group will not impact enrollment in the medium-dose group.

Participants from the Sentinel Cohort will receive their second vaccination (VAC2), 21 days after VAC1, if deemed appropriate after SMT data review of safety and reactogenicity data post VAC1. Participants in each the ultra-low-, low-, and medium-dose groups will receive their second vaccination in the same fashion as the first vaccination with intervening SMTs assessing early reactogenicity. Participants will be contacted by phone on D03 to collect D01-03 safety data and SMT evaluation for each group of Sentinel participants.

Complete Sentinel ESDR and Full Enrollment Cohort

The CS-ESDR-1 will be performed for all Sentinel Cohort participants after safety data, including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, is obtained from D01-D09 following the first injection. This unblinded review will be performed by the Sponsor during the SMT meeting. Progression to the Full Enrollment Cohort for selected or all of

[redacted]

the dose-levels will occur after CS-ESDR-1 with evaluation of safety data up to D09 post first vaccination in all Sentinel Cohorts participants.

If no safety signals or major tolerability concerns are identified at CS-ESDR-1, the double-blind enrollment of up to 308 participants (vaccine and placebo groups) for the first vaccination of the Full Enrollment Cohort (Cohort 1 allocated to the single-injection schedule and Cohort 2 allocated to the 2-injection schedule) will be initiated. It is to be noted that the first vaccination in the Full Enrollment Cohort may be delayed until after the second vaccination of some of the Sentinel Cohort groups or even postponed until after CS-ESDR-2, if deemed necessary by the SMT.

After CS ESDR-1, participants in Cohort 1 will receive their injection of study intervention while participants in Cohort 2 will receive the first of 2 injections of the study intervention at D01 (VAC1).

A subsequent safety review (CS-ESDR-2) is planned for all Sentinel Cohort participants during which the unblinded SMT will examine the available D22-D30 safety data post-second vaccination including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, and all available MAAEs, SAEs, and AESIs for the Sentinel Cohort participants will also be reviewed. If no safety signals or major tolerability concerns are identified during this period in the Sentinel Cohort, then all participants in Cohort 2 will progress to get the second injection (VAC2). If a safety signal or a major tolerability concern is identified at CS-ESDR-2 for the Sentinel Cohort, then Cohort 2 participants for the corresponding dose-level may not receive their second vaccination.

It should be noted that throughout the study, the SMT core members, consisting of Clinical Team Leader (Responsible Medical Officer [RMO]), Study Biostatistician, Pharmacovigilance Science Expert, and Global Safety Officer, will continuously review blinded safety data, except for the safety reviews for the Sentinel Cohort and the planned interim analyses, during which unblinded safety data will be reviewed. The blind will be broken at the group level for the Sponsor at the time of each interim analysis. Further unblinding may be necessary if any of the halting rules are met (see Section 8.4.3) or if there is any safety concern.

Participants follow-up

Participants will be followed over the duration of the study for development of symptoms of COVID-19-like illness. Participants will receive surveillance phone calls every 2 weeks (± 6 days, starting after the D43 contact to approximately 6 months) or may be contacted through alternative contact methods (text messages, email, and/or home visit) to enquire about the development of symptoms of COVID-19-like illness and to remind the participants to contact study staff if they experience symptoms of COVID-19-like illness. In addition, all participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study. The reporting of events temporally associated with COVID-19-like illness are outlined in Table 1.6.

Duration of participation in the study

The duration of each participant's participation in the study will be approximately 365 days post-last injection:

- Sentinel Cohort: approximately 386 days duration total

[redacted]

- Cohort 1 of Full Enrollment Cohort: approximately 365 days duration total
- Cohort 2 of Full Enrollment Cohort: approximately 386 days duration total

Authorized for emergency use and Approved SARS-CoV-2 vaccines

If an authorized for emergency use/approved SARS-CoV-2 vaccine is available in the country or region where the study is conducted, investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized SARS-CoV-2 vaccine if applicable to them. Recruitment and enrollment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at least until completion of the key follow-up timepoint (D43) of this study for informing progression to further clinical development and dose selection.

If the participant is enrolled and seeks vaccination of an authorized/approved 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 any time. If the participant receives the authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved COVID-19 vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants will be invited to a visit prior to receiving the vaccine and requested to provide a blood sample for immunological assessment. Participants will not receive the second vaccination if they have received the authorized/approved COVID-19 vaccine between the first and second scheduled vaccination.

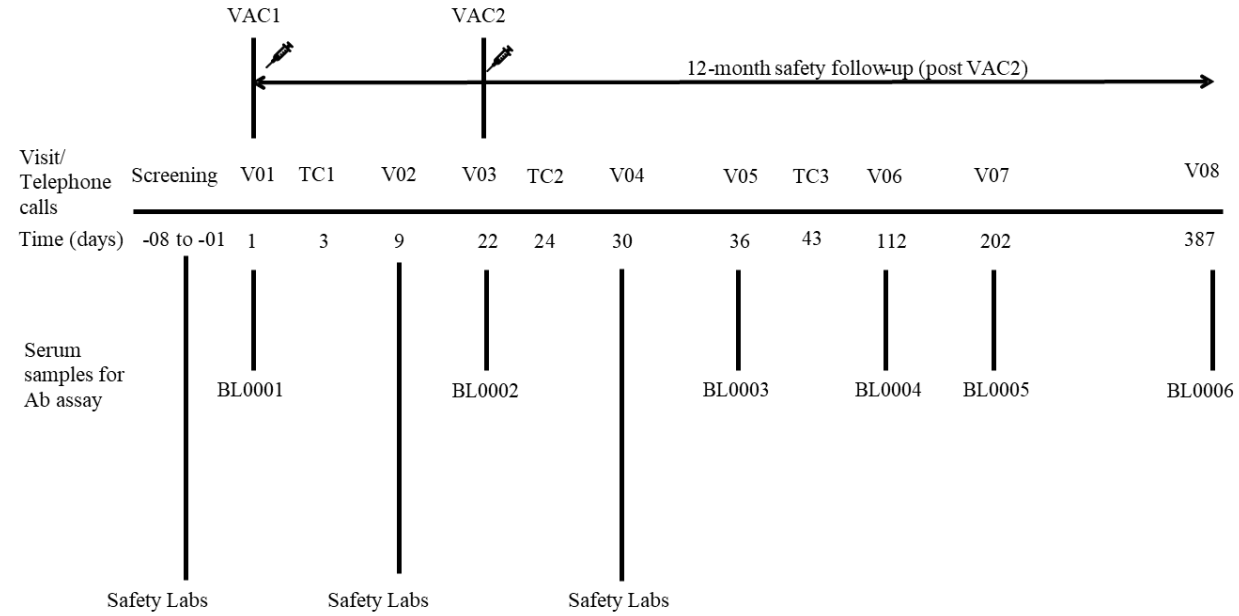
Data Monitoring Committee: **No**

1.2 Schema

The graphical design of VAW00001 study is presented in Figure 1.1 (for Sentinel Cohort), Figure 1.2 (for Cohort 1 of Full Enrollment Cohort), and Figure 1.3 (for Cohort 2 of Full Enrollment Cohort). The graphical design for the Sentinel Cohort dose-escalation and CS-ESDR timeline and enrollment of the original Protocol version 2.0 is presented in Figure 1.4. The lightning symbol indicates when the study was paused and the protocol amended. The updated graphical design for the Sentinel Cohort, including both the ultra-low-dose group and the possible Expanded Sentinel Cohort groups, is presented in Figure 1.5.

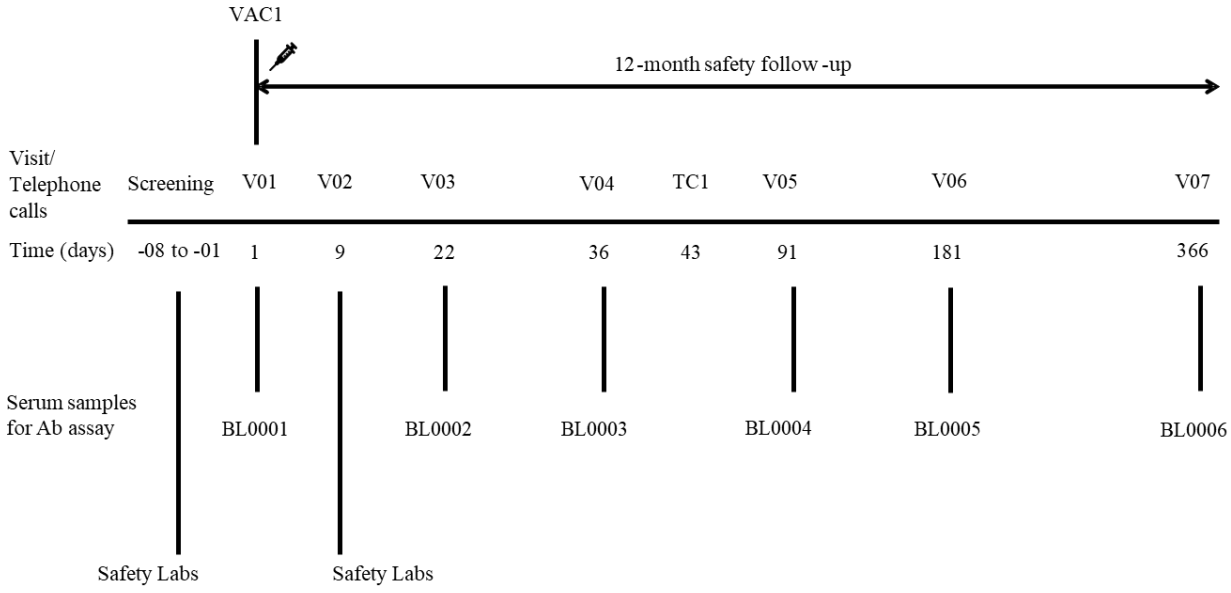
[redacted]

Figure 1.1: Graphical study design (Sentinel Cohort; Initial and Expanded)



Ab, antibody; BL, blood sample (#); TC, telephone call; V, visit, VAC, Vaccination

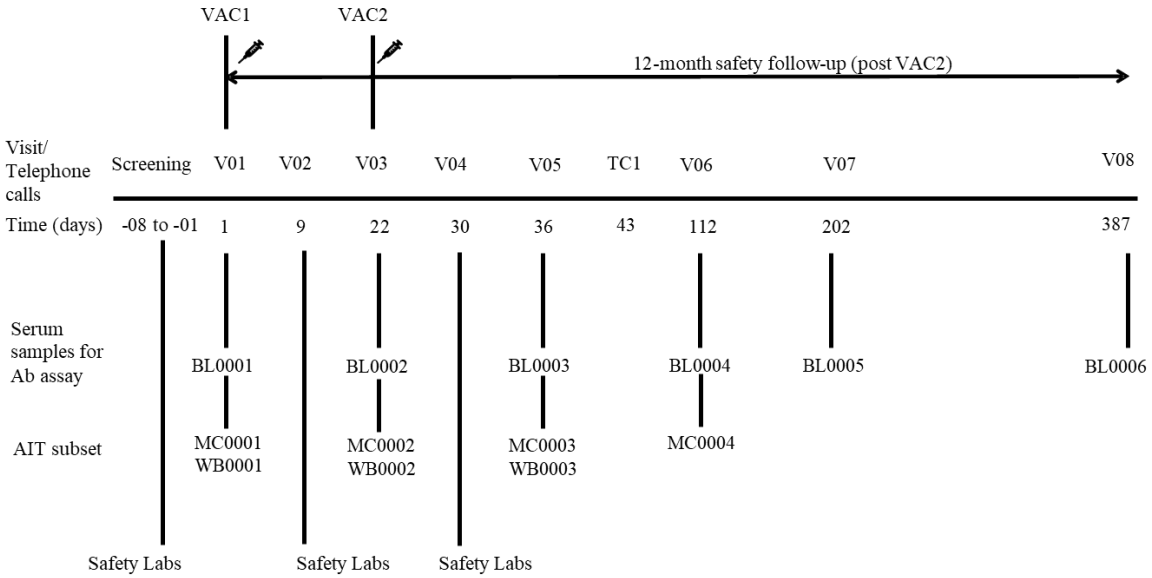
Figure 1.2: Graphical study design (Cohort 1 of Full Enrollment Cohort)



Ab, antibody; BL, blood sample (#); TC, telephone call; V, visit, VAC, Vaccination

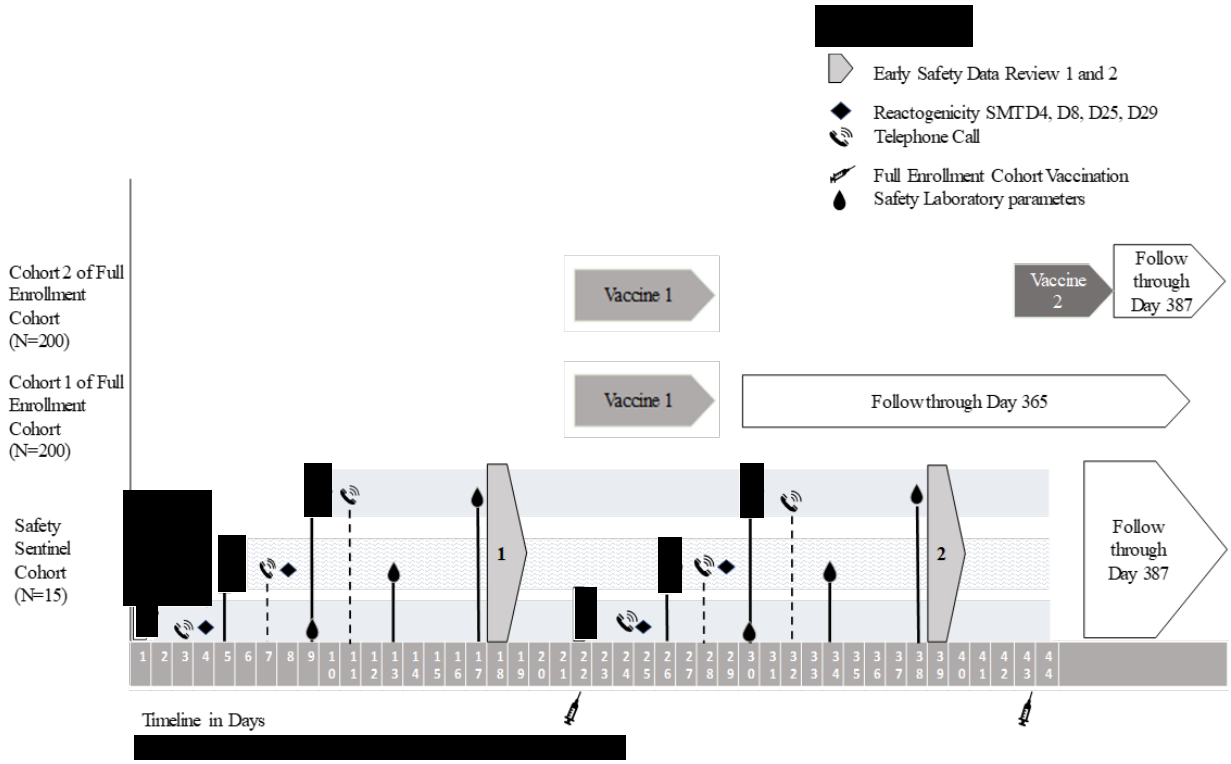
[redacted]

Figure 1.3: Graphical study design (Cohort 2 of Full Enrollment Cohort)



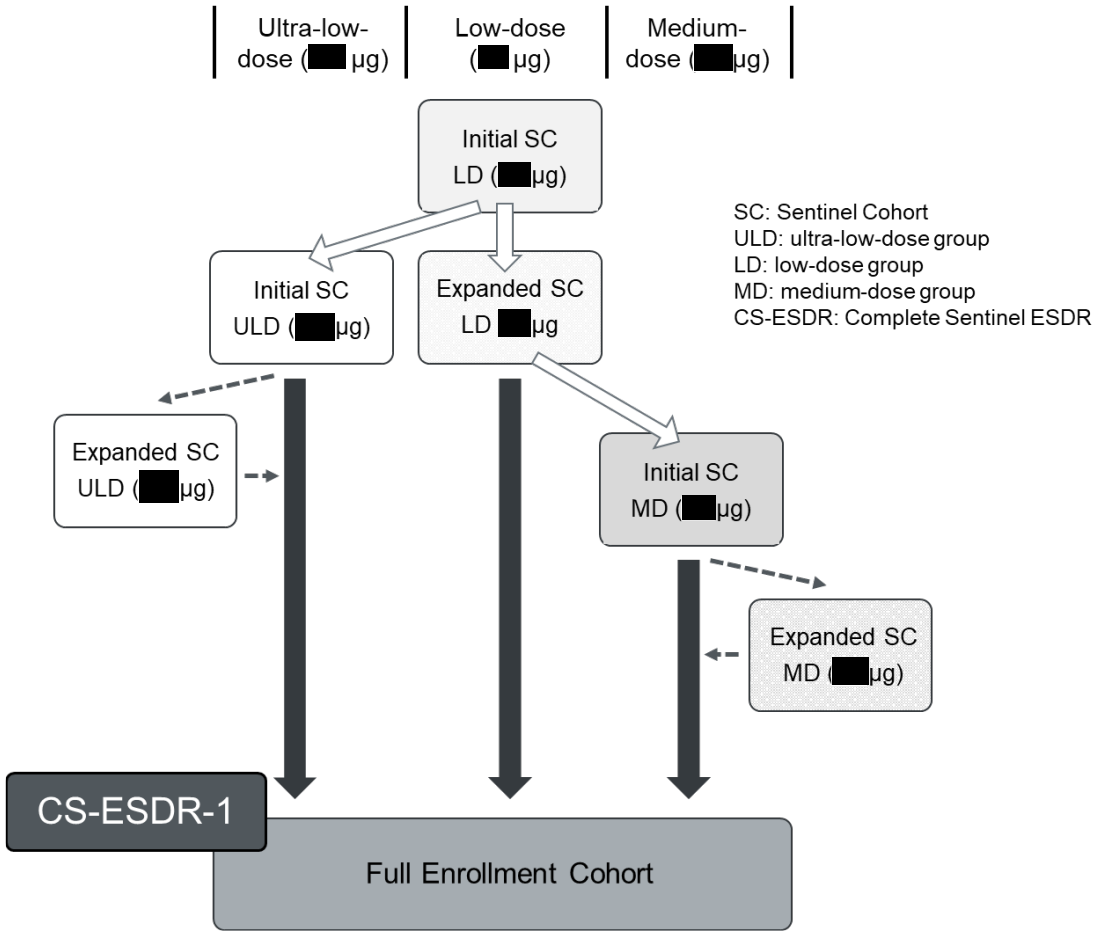
Ab, antibody; BL, blood sample (#); AIT, Additional Immunological Tests; MC, mononuclear cell; TC, telephone call; V, visit; VAC, vaccination; WB, whole blood,

Figure 1.4: Previous Graphical design for Sentinel Cohort dose-escalation and Early Safety Data Review (Original Protocol version 2.0)



[redacted]

Figure 1.5: Current Graphical design for Sentinel Cohort



1.3 Schedule of Activities (SoA)

Visits procedures are detailed in the Operating Guidelines.

[redacted]

Table 1.3: Schedule of activities 1 (Sentinel Cohort, Initial and Expanded)

Phase I/II Study, 8 Visits after Enrollment, 3 Telephone Calls, 2 Injections, 6 Blood Sample Time-points for Immunogenicity, Approximately 13 Months Duration Per Participant

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** ††††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
Informed consent for enrollment	*X*	X											
Point-of-care SARS-CoV-2 antibody test (1 mL) ††		X											
Inclusion/exclusion criteria	*X*	X	X										
Collection of demographic data	*X*	X											
Collection of medical history	*X Significant Medical History*	X	X										

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** ††††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
Physical examination*		X	X										
Pre-vaccination temperature			X			X							
Urine pregnancy test (if applicable)†		X	X			X							
Contact IRT system for screening/participant number allocation	*X*	X											
Contact IRT system for unique dose number allocation	*X*		X			X							
Temporary and definitive contraindications	*X*					X							
Respiratory sample collection			Can occur at any time during the study as unscheduled visit(s) (See also Schedule of Activities Table 1.6)										

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** †††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
Clinical safety laboratory assessments‡ (~15 mL)	*X*	X			X			X					
Serum samples for Ab assays (30 mL)§	*X*		BL0001**			BL0002**			BL0003		BL0004	BL0005	BL0006
HIV, Hepatitis B, Hepatitis C serology†† (~5 mL)		X											
Vaccination	*X*		X *(VAC1)*			X *(VAC2)*							
Immediate surveillance (30 minutes)	*X*		X			X							
Diary Card provided			DC1‡‡			DC2†††			DC3‡‡‡		DC4§§§	DC5****	
Diary Card reviewed				DC1§§	DC1§§		DC2§§	DC2§§		DC3§§			
Diary Card collected						DC1***			DC2***		DC3***	DC4***	DC5***

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** ††††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
Collection of solicited injection site and systemic reactions	*X*		D01-D08 *(up to 7 days post-VAC1)*			D01-D08 *(up to 7 days post-VAC2)*							
Collection of unsolicited AEs	*X*		D01-D22 *(up to 21 days post-VAC1)*										
						D01-D22 *(up to 21 days post-VAC2)*							
Collection of concomitant medications	*X* *Reportable concomitant medication*		All reportable concomitant medications (including influenza and COVID-19 vaccination other than the study vaccine)								Only influenza and COVID-19 vaccination, and any COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma)		
Telephone call	*X*			X††††			X††††			X††††			X††††††
Passive surveillance	*X*		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study (See also Schedule of Activities Table 1.6)										

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** ††††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
Active surveillance calls	*X*									TC to occur every 2 weeks (± 6 days) after the D43 contact until D202‡‡‡‡ (See also Schedule of Activities Table 1.6 for follow-up)			
Collection of SAEs, AESIs§§§§, and MAAEs	*X*		To be reported at any time during the study										
Collection of pregnancies	*X*												
End of phase participation record*****	*X*									X	X	X	
End of active phase participation record	*X*												X
12 month post-VAC2 follow-up participation record (only for those	*X*												X

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**TC1**	**V02**	**V03**	**TC2**	**V04**	**V05**	**TC3**	**V06**	**V07**	**V08** ††††††
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D03	D09	D22	D24	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 2 days	V01 + 8 days	V01 + 21 days	V03 + 2 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	N/A	[+2 days]	[+7 days]	N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:													
discontinued early) †††††													

Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, Case Report Form; D, Day; DC, Diary Card; HIV, human immunodeficiency virus; IRT, Interactive Response Technology; MAAE, medically attended AE; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, telephone call; V, Visit; VAC, Vaccination.

* Targeted physical examination will be performed at screening. If needed, targeted physical examination based on medical history and Investigator's discretion might be performed at V01.

† Female participants of childbearing potential must have a negative urine pregnancy test prior to administration of study product. Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). Urine pregnancy test is to be performed at screening (performed within -D04 and -D01) and before vaccinations.

‡ Safety laboratory assessments will include: serum chemistries (including liver enzymes and renal function); hematology (complete blood count with differential) and coagulation times (PT and PTT); urinalysis; Microscopy will be performed if urinalysis is abnormal. In cases of abnormal safety laboratory results, unscheduled visits may occur and laboratory tests may be checked based on Investigator's judgment. Assessment of clinical safety laboratory parameters at screening must be performed within -D04 to -D01.

§ If a participant seeks an authorized/approved COVID-19 vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment (UB0001).

** BL0001 will be collected at pre-vaccination (baseline). BL0002 sample will be collected prior to D22 vaccination.

†† Result of point-of-care SARS-CoV-2 antibody test must be obtained within -D04 to -D01.

Assessment of clinical safety laboratory parameters must be performed within -D04 to -D01.

Screening activities like COVID-19 antibody test and blood and urine sampling for safety tests may be performed on the day of enrollment as long as the results to assess exclusion criteria are available prior to enrollment.

Testing of HIV antibody, Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody must be obtained within -D08 to -D01. This testing will be performed at the study center using local accepted diagnostic tests. It is to be noted that results for the above-mentioned HIV and Hepatitis serology tests obtained outside the study within 4 weeks prior to V01 will be accepted.

‡‡ Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to V03.

§§ The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

*** The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

††† Participants will use this DC2 to record solicited reactions, unsolicited AEs, SAEs, and AESIs (from V03 to V04) and will continue to collect unsolicited AEs, SAEs, and AESIs (from V04 to V05).

‡‡‡ Participants will use this DC3 for unsolicited AE follow-up until D43, and SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V05 to V06.

§§§ Participants will use this DC4 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V06 to V07.

**** Participants will use this DC5 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V07 to V08.

†††† During the D43 telephone call, staff will review the DC3 pertaining to unsolicited AEs, SAE, AESI, and COVID-19-like illness between V05 and the call (data will be entered in the CRF) and will remind the participants to bring back the DC3 for V06. The D03 and D24 telephone calls will NOT be reported in the CRF (ie, only the data obtained from these telephone calls will be reported in the CRF).

‡‡‡‡ The frequency of phone contacts will be once every 2 weeks (± 6 days) or may be completed through alternative contact methods (text message, email, and/or home visit). Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits).

§§§§ AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causal relationship. These include protocol-specified AESIs: anaphylactic reactions, generalized convulsion, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, thrombocytopenia, vasculitides, any new-onset chronic medical conditions, and AESIs related to SARS-CoV-2 infection and COVID-19 disease.

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

††††† All participants will be scheduled to attend V08 for blood sampling and 12-Month (post-VAC2) Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the Safety Follow-up call.

Table 1.4: Schedule of activities 2 (Cohort 1 of Full Enrollment Cohort)

Phase I/II Study, 7 Visits after Enrollment, 1 Telephone Call, 1 Injection, 6 Blood Sample Time-points, approximately 12 Months Duration Per Participant

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**TC1**	**V05**	**V06**	**V07†††††**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D36	D43	D91	D181	D366
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 + 90 days	V01 + 180 days	V01 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Informed consent for enrollment	*X*	X								
Point-of-care SARS-CoV-2 antibody test (1 mL) ††		X								
Inclusion/exclusion criteria	*X*	X	X							
Collection of demographic data	*X*	X								
Collection of medical history	*X Significant Medical History*	X	X							
Physical examination*		X	X							
Pre-vaccination temperature			X							
Urine pregnancy test (if applicable)†		X	X							

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**TC1**	**V05**	**V06**	**V07†††††**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D36	D43	D91	D181	D366
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 + 90 days	V01 + 180 days	V01 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Contact IRT system for screening/participant number allocation	*X*	X								
Contact IRT system for randomization and unique dose number allocation	*X*		X							
Respiratory sample collection			Can occur at any time during the study as unscheduled visit(s) (See also Schedule of Activities Table 1.6)							
Clinical safety laboratory assessments‡ (~15 mL blood sample)	*X*	X		X						
Serum samples for Ab assays (30 mL) §	*X*		BL0001**		BL0002	BL0003		BL0004	BL0005	BL0006
HIV, Hepatitis B, Hepatitis C serology†† (~5 mL)		X								
Vaccination	*X*		X *(VAC1)*							
Immediate surveillance (30 minutes)	*X*		X							
Diary Card provided			DC1‡‡		DC2†††	DC3‡‡‡		DC4§§§	DC5****	
Diary Card reviewed				DC1§§			DC3§§			
Diary Card collected					DC1***	DC2***		DC3***	DC4***	DC5***

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**TC1**	**V05**	**V06**	**V07†††††**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D36	D43	D91	D181	D366
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 + 90 days	V01 + 180 days	V01 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Collection of solicited injection site & systemic reactions	*X*		D01-D08 *(up to 7 days post-VAC1)*							
Collection of unsolicited AEs	*X*		D01-D22 *(up to 21 days post-VAC1)*							
Collection of concomitant medications	*X Reportable concomitant medication*		All reportable concomitant medications (including influenza and COVID-19 vaccination other than the study vaccine)			Only influenza and COVID-19 vaccination, and any COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma)				
Telephone call	*X*						X††††			X†††††
Passive surveillance	*X*		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study (See also Schedule of Activities Table 1.6)							
Active surveillance calls	*X*						TC to occur every 2 weeks (± 6 days) after the D43 contact until D181‡‡‡‡			

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**TC1**	**V05**	**V06**	**V07†††††**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D36	D43	D91	D181	D366
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 + 90 days	V01 + 180 days	V01 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
							(See also Schedule of Activities Table 1.6 for follow-up)			
Collection of SAEs, AESIs§§§§, and MAAEs	*X*		To be reported at any time during the study							
Collection of pregnancies	*X*									
End of phase participation record*****	*X*						X	X	X	
End of active phase participation record	*X*									X
12 Month Follow-up participation record (only for those discontinued early)*****	*X*									X

Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, Case Report Form; D, Day; DC, Diary Card; HIV, human immunodeficiency virus; IRT, Interactive Response Technology; MAAE, medically attended adverse event; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, telephone call; V, Visit; VAC, vaccination.

* Targeted physical examination will be performed at screening. If needed, targeted physical examination based on medical history and Investigator's discretion might be performed at V01.

† Female participants of childbearing potential must have a negative urine pregnancy test prior to administration of study product. Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). Urine pregnancy test is to be performed at screening (performed within -D04 and -D01) and before vaccination.

‡ Safety laboratory assessments will include: serum chemistries (including liver enzymes and renal function); hematology (complete blood count with differential) and coagulation times (PT and PTT); urinalysis; microscopy will be performed if urinalysis is abnormal. In cases of abnormal safety laboratory results, unscheduled visits may occur and laboratory tests may be checked based on Investigator's judgment. Assessment of clinical safety laboratory parameters at screening must be performed within -D04 to -D01.

§ If a participant seeks an authorized/approved COVID-19 vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment (UB0001).

** BL0001 will be collected at pre-vaccination (baseline).

†† Result of point-of-care SARS-CoV-2 antibody test must be obtained within -D04 to -D01.

Assessment of clinical safety laboratory parameters must be performed within -D04 to -D01.

Screening activities like COVID-19 antibody test and blood and urine sampling for safety tests may be performed on the day of enrollment as long as the results to assess exclusion criteria are available prior to enrollment.

Testing of HIV antibody, Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody must be obtained within -D08 to -D01. This testing will be performed at the study center using local accepted diagnostic tests. It is to be noted that results for the above-mentioned HIV and Hepatitis serology tests obtained outside the study within 4 weeks prior to V01 will be accepted.

‡‡ Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to V03.

§§ The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

*** The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

††† Participants will use this DC2 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V03 to V04.

‡‡‡ Participants will use this DC3 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V04 to V05.

§§§ Participants will use this DC4 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V05 to V06.

**** Participants will use this DC5 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V06 to V07.

†††† During the D43 telephone call, staff will review the DC3 pertaining to SAE, AESI, and COVID-19-like illness between V04 and the call (data will be entered in the CRF) and will remind the participant to bring back the DC3 for V05.

‡‡‡‡ The frequency of phone contacts will be once every 2 weeks (± 6 days) or may be completed through alternative contact methods (text message, email, and/or home visit). Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits).

§§§§AESIs (serious and non-serious) will be collected through the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causal relationship. These include protocol-specified AESIs: anaphylactic reactions, generalized convulsion, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, thrombocytopenia, vasculitides, any new-onset chronic medical conditions, and AESIs related to SARS-CoV-2 infection and COVID-19 disease.

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

††††† All participants will be scheduled to attend V07 for blood sampling and 12-Month Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a 12-Month Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the 12-Month Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the 12-Month Safety Follow-up call.

Table 1.5: Schedule of activities 3 (Cohort 2 of Full Enrollment Cohort)

Phase I/II Study, 8 Visits after Enrollment, 1 Telephone Call, 2 Injections, 6 Blood Sample Time-points, approximately 13 Months Duration Per Participant

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**V05**	**TC1**	**V06**	**V07**	**V08‡‡‡‡‡**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:											
Informed consent for enrollment	*X*	X									
Point-of-care SARS-CoV-2 antibody test (1 mL) ††		X									
Inclusion/exclusion criteria	*X*	X	X								
Collection of demographic data	*X*	X									
Collection of medical history	*X Significant Medical History*	X	X								
Physical examination*		X	X								
Pre-vaccination temperature			X		X						
Urine pregnancy test (if applicable)†		X	X		X						

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**V05**	**TC1**	**V06**	**V07**	**V08‡‡‡‡‡**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:											
Contact IRT system for screening/participant number allocation	*X*	X									
Contact IRT system for randomization and unique dose number allocation	*X*		X								
Contact IRT system for unique dose number allocation	*X*				X						
Temporary and definitive contraindications	*X*				X						
Respiratory sample collection			Can occur at any time during the study as unscheduled visit(s) (See also Schedule of Activities Table 1.6)								
Clinical safety laboratory assessments‡ (~15 mL blood sample)	*X*	X		X		X					
Serum samples for Ab assays (30 mL)§	*X*		BL0001**		BL0002**		BL0003		BL0004	BL0005	BL0006
HIV, Hepatitis B, Hepatitis C serology†† (~5 mL)		X									

[redacted]

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**V05**	**TC1**	**V06**	**V07**	**V08‡‡‡‡‡**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:											
AIT (40 mL) and TruCulture (4 mL) *(Subset of up to 77 participants)* ‡‡	*X*		MC0001** WB0001**		MC0002** WB0002**		MC0003 WB0003		MC0004		
Vaccination	*X*		X *(VAC1)*		X *(VAC2)*						
Immediate surveillance (30 minutes)	*X*		X		X						
Diary Card provided			DC1§§		DC2‡‡‡		DC3§§§		DC4****	DC5††††	
Diary Card reviewed				DC1***		DC2***		DC3***			
Diary Card collected					DC1†††		DC2†††		DC3†††	DC4†††	DC5†††
Collection of solicited injection site & systemic reactions	*X*		D01-D08 *(up to 7 days post-VAC1)*		D01-D08 *(up to 7 days post-VAC2)*						
Collection of unsolicited AEs	*X*		D01-D22 *(up to 21 days post-VAC1)*								
					D01-D22 *(up to 21 days post-VAC2)*						
Collection of concomitant medications	*X* *Reportable concomitant medication*		All reportable concomitant medications (including influenza and COVID-19 vaccination other than the study vaccine)						Only influenza and COVID-19 vaccination, and any COVID-19 prophylaxis (eg, SARS-CoV-2		

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**V05**	**TC1**	**V06**	**V07**	**V08‡‡‡‡‡**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:											
									antivirals, monoclonal antibodies, plasma)		
Telephone call	*X*							X‡‡‡‡			X††††††
Passive surveillance	*X*		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study (See also Schedule of Activities Table 1.6)								
Active surveillance calls	*X*							TC to occur every 2 weeks (± 6 days) after the D43 contact until D202§§§§ (See also Schedule of Activities Table 1.6 for follow-up)			
Collection of SAEs, AESIs*****, and MAAEs	*X*		To be reported at any time during the study								
Collection of pregnancies	*X*										
End of phase participation record††††††	*X*							X	X	X	
End of active phase participation record	*X*										X
12 month post-VAC2 follow-up participation record (only	*X*										X

Visit (V)/Contact	*Collection of information in the CRF*	**Screening visit**	**V01**	**V02**	**V03**	**V04**	**V05**	**TC1**	**V06**	**V07**	**V08‡‡‡‡‡**
Study timelines (Day [D])		D(-08) to D(-01)††	D01	D09	D22	D30	D36	D43	D112	D202	D387
Time interval (days)		V01 – (1 to 8 days)		V01 + 8 days	V01 + 21 days	V03 + 8 days	V03 + 14 days	V03 + 21 days	V03 + 90 days	V03 + 180 days	V03 + 365 days
Time windows (days)			N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:											
for those discontinued early) ‡‡‡‡‡											

Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; AIT, Additional Immunological Tests; BL, blood sample (#); CRF, Case Report Form; D, Day; DC, Diary Card; HIV, human immunodeficiency virus; IRT, Interactive Response Technology; MAAE, medically attended AE; MC, mononuclear cell; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, telephone call; V, Visit; VAC, Vaccination; WB, whole blood.

* Targeted physical examination will be performed at screening. If needed, targeted physical examination based on medical history and Investigator's discretion might be performed at V01.

† Female participants of childbearing potential must have a negative urine pregnancy test prior to administration of study product. Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). Urine pregnancy test is to be performed at screening (performed within -D04 and -D01) and before vaccinations.

‡ Safety laboratory assessments will include: serum chemistries (including liver enzymes and renal function); hematology (complete blood count with differential) and coagulation times (PT and PTT); urinalysis; microscopy will be performed if urinalysis is abnormal. In cases of abnormal safety laboratory results, unscheduled visits may occur and laboratory tests may be checked based on Investigator's judgment. Assessment of clinical safety laboratory parameters at screening must be performed within -D04 to -D01.

§ If a participant seeks an authorized/approved COVID-19 vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment (UB0001).

** BL0001, MC0001, and WB0001 samples will be collected at pre-VAC1 (baseline). BL0002, MC0002, and WB0002 samples will be collected at pre-VAC2.

†† Result of point-of-care SARS-CoV-2 antibody test must be obtained within -D04 to -D01.

Assessment of clinical safety laboratory parameters must be performed within -D04 to -D01.

Screening activities like COVID-19 antibody test and blood and urine sampling for safety tests may be performed on the day of enrollment as long as the results to assess exclusion criteria are available prior to enrollment.

Testing of HIV antibody, Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody must be obtained within -D08 to -D01. This testing will be performed at the study center using local accepted diagnostic tests. It is to be noted that results for the above-mentioned HIV and Hepatitis serology tests obtained outside the study within 4 weeks prior to V01 will be accepted.

‡‡ If a participant seeks an authorized/approved COVID-19 vaccine at or after D50 but before D112, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for assessment (UM0001).

§§ Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to V03.

*** The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

††† The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

‡‡‡ Participants will use this DC2 to record solicited reactions, unsolicited AEs, SAEs, and AESIs (from V03 to V04) and will continue to collect unsolicited AEs, SAEs, and AESIs (from V04 to V05).

§§§ Participants will use this DC3 for unsolicited AE follow-up until D43, and SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V05 to V06.

**** Participants will use this DC4 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V06 to V07.

†††† Participants will use this DC5 for SAE follow-up (including AESIs) and COVID-19-like illness follow-up from V07 to V08.

‡‡‡‡ During the D43 telephone call, staff will review the DC3 pertaining to unsolicited AEs, SAE, AESI, and COVID-19-like illness between V05 and the call (data will be entered in the CRF) and will remind the participants to bring back the DC3 for V06.

§§§§The frequency of phone contacts will be once every 2 weeks (± 6 days) or may be completed through alternative contact methods (text message, email, and/or home visit). Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits).

*****AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causal relationship. These include protocol-specified AESIs: anaphylactic reactions, generalized convulsion, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, thrombocytopenia, vasculitides, any new-onset chronic medical conditions, and AESIs related to SARS-CoV-2 infection and COVID-19 disease.

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

‡‡‡‡‡ All participants will be scheduled to attend V08 for blood sampling and 12-Month (post-VAC2) Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the Safety Follow-up call.

Table 1.6: Schedule of activities 4 (Follow-up of COVID-19-like illness)

Contact Type	Initial Telephone Call*	Visit	Follow-up Telephone Call†
Verify information on COVID-19-like illnesses and schedule appointment for collection of respiratory samples as soon as possible after illness start date‡	X		
Collection of information on respiratory illness symptoms	X	X	X
Remind participant to complete Memory Aid or Diary Card	X	X	X
Collection of respiratory specimen		NPXXXX§	
Collection of disease burden and health care information	X	X	X
Collection of treatments received during COVID-19-like illness	X	X	X

* Initial illness identification phone call. During the illness episode, participants may be contacted by the site staff for medical monitoring. The frequency of contact for medical monitoring is at the discretion of the investigator.

† Follow-up telephone call approximately 30 days after onset of illness

‡ Start of first clinical manifestation of COVID-19-like illness, unless during the first reactogenicity period (D01-D09) when the sample may be collected up to D09, at the Investigator's discretion.

§ "X" indicates that the nasopharyngeal swab number will be unique to each site. Further details are provided in the Operating Guidelines. A nasopharyngeal swab for central laboratory testing will be collected. A sample for local laboratory testing (clinical care) may be collected in addition to the NP swab for central laboratory testing. The swab will not be collected during a CLI visit if the date of collection is more than 14 days after resolution of symptoms.

2 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that emerged in the human population and has led to a pandemic of acute respiratory disease named COVID-19. Coronaviruses are a family of large, enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses that infect a wide variety of mammalian and avian species. In the last 20 years, 3 zoonotic coronaviruses are known to have crossed species to cause SARS in humans, which include SARS-CoV, SARS-CoV-2, and the more distantly related Middle East Respiratory Syndrome coronavirus (MERS-CoV) (3). Coronavirus entry into the host cells is mediated by the transmembrane spike (S) glycoprotein which permits both the binding to the host cell receptor (via the S1 subunit) and the fusion of viral and cellular membranes (via the S2 subunit). Recent work has shown that the SARS-CoV-2 receptor binding gene region is similar to SARS-CoV and uses the same receptor, angiotensin-converting enzyme 2 on the human cell surface (4).

Prior research with MERS-CoV identified that the introduction of double proline substitutions (2P) at the beginning of the central helix of the S2 subunit could stabilize the structure and prevent conformational changes in the S trimer (5). When used to immunize mice, the MERS-CoV 2P construct was associated with improved breadth and potency of neutralizing responses compared to monomeric MERS-CoV S1 or wild-type S. This strategy was identified as being of general relevance to betacoronaviruses, which include Human Coronavirus (HCoV)-NL63, MERS-CoV, and SARS-CoV-1, and by extrapolation to SARS-CoV-2 (6). The prefusion stabilized SARS-CoV-2 S construct to be evaluated in the current study is based on this research.

To address the urgent medical need caused by the COVID-19 outbreak, Sanofi Pasteur is developing a SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine consisting of an mRNA encoding the full-length sequence for the prefusion stabilized form of the SARS-CoV-2 surface S protein with 2 sets of mutations, one set (2P) in the S2 portion of the S protein that locks the expressed S protein in the prefusion conformation, and second set (GSAS) at the S1/S2 cleavage site which prevents the cleavage of the expressed protein into the S1 and S2 subunits. The mRNA vaccine is complexed with a novel lipid nanoparticle (LNP) vehicle [redacted]. Prior to this study, neither the LNP nor the mRNA targeted in this study have been administered to humans before. However, studies with the SARS-CoV-2 mRNA vaccine in rabbits [redacted], mice [redacted], hamsters [redacted], and non-human primates (NHP; [redacted]) support the safety, immunogenicity, and protective efficacy of this vaccine (for more details see the Investigator's Brochure). The investigational vaccine candidate uses a technology platform developed with an ongoing collaboration between Translate Bio and Sanofi Pasteur and will be manufactured by Translate Bio.

A potential safety issue with coronavirus vaccines is the ability to potentiate immunopathological manifestations in vaccinees upon further exposure to wild-type virus (7). The molecular mechanism for this immunopathogenesis is not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the

[redacted]

immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the T-helper (Th) cell response (8) (9) (10). It is anticipated that the design of the candidate SARS-CoV-2 mRNA vaccine selected for this study will promote the generation of neutralizing antibodies over binding antibodies, based on data generated with other coronavirus vaccine antigens (5) (6) and mRNA vaccines may be inclined to produce a favorable Th1/Th2 response, likely predominantly Th1 biased (11). Taken together, these strategies are designed to mitigate the theoretical risks of immune enhancement of viral infection.

The initial intended use of the SARS-CoV-2 mRNA vaccine is for adults, 18 years of age and older. It is planned that studies to support use of the vaccine in children 6 months to 17 years of age will be conducted after the initial data from studies in adults are available.

2.1 Study Rationale

VAW00001 is a first-in-human Phase I/II, multi-center study comprised of 2 sequential cohorts: a lead-in open-label Sentinel Cohort, followed by a randomized, modified double-blind, dose-ranging, placebo-controlled Full Enrollment Cohort, to evaluate the safety and immunogenicity of the SARS-CoV-2 mRNA vaccine, in healthy adult participants (18 years of age and older) in the United States (US) and Honduras. In its original design, the study was to evaluate 3 different dose-levels [redacted] of the candidate mRNA vaccine with the goal of selecting the optimal dose and schedule to proceed to a Phase III study. [redacted]

Further considerations of the safety data from the 5 participants assigned to the low-dose level group revealed the transient nature of the reported Grade 3 adverse events. Given the fact that these AEs were self-limited (ie, no subject sought any medical attention) and no major safety concerns were identified, the Sponsor decided to introduce 4 changes through a protocol amendment:

1) add a “ultra-low-dose” arm of [redacted] µg [redacted] intended to evaluate [redacted] a lower dose-level range (ie, ultra-low- [redacted] µg], low- [redacted] µg], and medium- [redacted] µg] dose-levels);
2) increase the number of Sentinel Cohort participants from 5 to 10 in the dose-level groups that have yet to start enrollment (ie, [redacted] µg and [redacted] µg);
3) add an expansion of the open-label Sentinel Cohort for the [redacted] µg dose-level to better understand the reactogenicity at this dose-level in a larger group of participants prior to escalation to the [redacted] µg dose. This possibility to expand the number of Sentinel Cohort participants will also be extended to the ultra-low- and medium-dose groups if needed;
4) decrease the number of placebo recipients in the Full Enrollment Cohort.

The longer-term objective remains to longitudinally define the safety and durability of the immune response induced by the SARS-CoV-2 mRNA vaccine over the 1 year study duration.

[redacted]

2.2 Background

The burden of SARS-CoV-2 morbidity and mortality has been catastrophic with greater than 2.8 million deaths recorded since first emerging in December 2019 among over 129 million confirmed cases (as of 02 April 2021) (2). In many locations, the rapid emergence of COVID-19 has overwhelmed the capacity of health systems to provide care for COVID-19-affected patients, let alone unaffected patients. Interventions to reduce transmission through reduction of population contact has had drastic economic consequences. At present, 2 COVID-19 mRNA vaccines, BNT162b2 from Pfizer and BioNTech and mRNA-1273 from Moderna, and 2 viral vector vaccines, ChAdOx1-nCOV-19 from Oxford University/AstraZeneca and Janssen COVID-19 vaccine (Ad26.COV2.S) from Johnson & Johnson have reported efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (12) (13) (14) (15). Emergency authorization or other forms of regulatory approval for these and additional other SARS CoV-2 vaccine candidates have been granted in multiple countries for the prevention of COVID-19. Given the ongoing medical and societal burden caused by SARS CoV2 infections, developing safe and effective vaccines remains a vital tool to address the global pandemic. The circulating virus has continued to evolve with the emergence of highly transmissible SARS CoV-2 variants of concern impeding the control of new infections. No single vaccine company could meet the needs for a worldwide vaccination strategy and continued vaccine development is crucial.

The clinical profile of COVID-19, the illness caused by SARS-COV-2, is variable and our understanding about its clinical profile is evolving (16). Asymptomatic infections appear frequent but prospective longitudinal studies are lacking. Some individuals who are initially asymptomatic may with time progress to recognizable symptoms, especially if monitored closely (17). The spectrum of symptomatic disease can vary from mild and without pulmonary involvement to life-threatening and fatal disease. In a report from the Chinese Center for Disease Control and Prevention describing 44 672 confirmed cases, disease severity was reported as 81% mild, 14% severe, and 5% critical in adults. The overall case fatality rate is reported as 2.3% but as high as 49% for those with critical illness (18). Typical initial symptomatic disease is characterized by fever, respiratory symptoms including cough and dyspnea, and fatigue, and are not easily distinguishable from other viral respiratory infections. Among hospitalized patients, symptoms may progress rapidly within a week to worsening hypoxia and pneumonia, severe respiratory compromise requiring mechanical ventilatory support, shock, cardiac injury, thromboembolic events, and death. In severe disease, a hyperinflammatory syndrome notable for cytokine release of proinflammatory cytokines has been appreciated and associated with severe illness and fatal outcome (19). Adults over 50 years of age and individuals with comorbidities like cardiovascular disease, diabetes mellitus, hypertension, obesity, and underlying pulmonary disease are at increased risk of adverse outcomes.

Emerging trends in vaccine development have focused on using mRNA technology to make novel vaccine candidates. This unique technology features engineered mRNA encoding an antigen of interest that is packaged and delivered to human target cells. The mRNA is encapsulated within an LNP which protects the mRNA from degradation and promotes fusogenicity and the efficient uptake of the LNP-mRNA complex within the target cell (20). Once internalized into the cell, the mRNA sequence is released from within the LNP into the cytoplasm, translated into protein by the human cell's own machinery, and post-translationally modified resulting in a properly folded

[redacted]

protein for antigen presentation. The mRNA vaccine and LNP are considered intrinsically immunogenic, thus, obviating the need for additional adjuvant enhancement.

The mRNA vaccines could demonstrate significant advantages over traditional vaccines. These advantages include 1) shorter manufacturing time, 2) rapid development of new targets, 3) cell free development with no infectious elements used in their manufacturing process, and 4) potential to include multiple immunogens in the same vaccine. However, the challenges with mRNA vaccines are that 1) the mRNA has to be protected from nuclease degradation until the mRNA can be translated into protein, 2) there is a need to assure enough mRNA gets translated into the antigen of interest, 3) the long term safety and immunogenicity are not yet well established, and 4) thermal stability may be limited with storage requiring infrastructure to maintain cold chain with present vaccines in study.

Further details of the chemistry, pharmacology, and safety of the SARS-CoV-2 mRNA vaccine are provided in the IB.

2.3 Benefit/Risk Assessment

While mRNA vaccines for infectious diseases have been generally well tolerated, the safety profile of mRNA vaccines is influenced by the LNP (21) (22). The investigational vaccine is complexed with a novel LNP vehicle [redacted]. The safety and immunogenicity of the LNP [redacted] was initially tested at Sanofi Pasteur in both mouse and NHP models using mRNA encoding influenza hemagglutinin (HA) where it was found to be well tolerated and induced potent HA neutralizing antibodies. Dose-ranging studies in New Zealand White rabbits using an influenza antigen and the candidate LNP supported the safety of LNP for the range of mRNA doses selected for this study (refer to the IB). Therefore, the early nonclinical safety data generated for the LNP with influenza mRNA is supportive for the tolerability of our SARS-CoV-2 mRNA vaccine candidate. A subsequent repeat dose toxicity study showed 3 intramuscular (IM) injections of the SARS-CoV-2 mRNA vaccine at 3 weeks interval, up to the dose level of [redacted] µg mRNA/injection were locally and systemically well tolerated (refer to the IB for details). In preclinical studies, SARS-CoV-2 mRNA vaccine induced dose-dependent S-specific binding and neutralizing antibody response with Th1-biased cellular responses in the mouse and NHP animal models (23).

A potential safety issue with coronavirus vaccines is the ability to potentiate immunopathological manifestations in vaccinees upon further exposure to wild-type virus. The potential for a coronavirus vaccine to exacerbate disease is a theoretical concern that has not been documented to date, but that will be explained as a theoretical risk in the informed consent document and will be monitored throughout the study.

The efficacy of the candidate vaccine has not been established. SARS-CoV-2 mRNA vaccine benefit/risk profile is expected to be positive based on available evidence. Study participation and study conduct is considered fundamental from the societal perspective towards the goal of finding a vaccine to help control the pandemic and decrease individual and public health burden of COVID-19 illness and SARS-CoV-2 infection.

[redacted]

The SARS-CoV-2 mRNA vaccine offers the potential of protection against SARS-CoV-2 infection and COVID-19 disease and its complications with a clinical benefit of reduction of the associated burden of disease in a population 18 years of age and older.

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of SARS-CoV-2 mRNA vaccine may be found in the SARS-CoV-2 mRNA IB.

[redacted]

2.3.1 Risks from Study Participation

The potential risks of clinical significance with respect to administration and vaccination of the SARS-CoV-2 mRNA vaccine are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: SARS-CoV-2 mRNA vaccine		
Anaphylactic reactions	Class-effect for all vaccines (even non-adjuvanted) (24)	Observation period after vaccination for early detection and treatment. Risk management will also be based on Exclusion criterion E07 (see Section 5.2.1 and Section 5.2.2).
Enhanced COVID-19	A theoretical safety issue with coronavirus vaccines is the ability to potentiate the frequency and severity of the clinical manifestations of COVID-19 in vaccinees upon further exposure to wild-type virus (7). The molecular mechanism for this immunopathogenesis is not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th response (8) (9) (10).	COVID-19-like illness will be part of the efficacy objective with active and passive surveillance. It is anticipated that the design of the candidate SARS-CoV-2 mRNA vaccine selected for this study will: • Promote the generation of neutralizing antibodies over binding antibodies, based on data generated with other coronavirus vaccine antigens (5) (6). • Produce a favorable T-helper (Th)1/Th2 response, likely predominantly Th1 biased (11). Individuals with chronic comorbid conditions considered to be associated with an increased risk of severe COVID-19 will be excluded as a strategy to mitigate the potential

[redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		risk of disease enhancement (25). Taken together, these strategies are designed to mitigate the theoretical risks of immune enhancement of viral infection.
Refer to IB Section 6 for more information regarding potential risks.	Refer to the IB Section 4 for more information regarding the data from previous non-human experience with the LNP.	
Study Procedures		
Vasovagal reactions (near-syncope or 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 vaccination for early detection and treatment.
Theoretical risk that participant can be exposed to other 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.	Study sites are to set up appropriate infection control measures to prevent participants from getting exposed during the study visits. Details to be described in the operating procedures. 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.

[redacted]

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 is considered fundamental from the societal perspective towards the goal of finding a vaccine to help control the pandemic and decrease individual and public health burden of COVID-19 illness and SARS-CoV-2 infection.

2.3.3 Overall Benefit-Risk Conclusion

Considering the significant medical need, scale of the pandemic, urgent requirement for measures to curb the disease, together with actions taken to minimize risk to participants enrolled in the study, there is no unreasonable and significant risk of illness or injury for the participants.

3 Objectives and Endpoints

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

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Primary	
Safety To describe the safety profile of all participants in each age group and each study intervention group up to 12 months post-last dose.	***Safety*** • Presence of unsolicited systemic AEs reported in the 30 minutes after each injection • Presence of solicited injection site reactions and systemic reactions (pre-listed in the participant's Diary Card [DC] and Case Report Form [CRF]) occurring up to 7 days after each injection • Presence of unsolicited AEs reported up to 21 days after each injection • Presence of medically attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study • Presence of out-of-range biological test results up to 8 days post-last dose (ie, up to Day [D] 09 for Cohort 1 and up to D30 for Sentinel Cohort and Cohort 2)

[redacted]

Objectives	Endpoints
Immunogenicity To describe the neutralizing antibody profile at D01, D22, and D36 of each study intervention group.	***Immunogenicity*** Neutralizing antibody titers against the SARS-CoV-2 D614G variant will be measured with the neutralization assay • Antibody titer at D01, D22, and D36 • Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36 • 2-fold and 4-fold-rise in serum neutralization titer (post/pre) relative to D01 at D22, and D36 • Occurrence of neutralizing antibody seroconversion defined as baseline values below lower limit of quantification (LLOQ) with detectable neutralization titer above assay LLOQ at D22 and D36
Secondary	
Immunogenicity 1) To describe binding antibody profile at D01, D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) of each study intervention group. 2) To describe the neutralizing antibody profile at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) of each study intervention group.	***Immunogenicity*** Binding antibody titers to trimerized SARS-CoV-2 S protein will be measured for each study intervention group with the enzyme-linked immunosorbent assay (ELISA) method • Individual anti-S antibody concentration at D01, D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Individual anti-S antibody concentration ratio (fold-rise in serum ELISA concentration post-vaccination relative to D01) at D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Fold-rise in anti-S antibody concentration (post/pre) ≥ 2 and ≥ 4 at D22, D36, D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) Neutralizing antibody titers against the SARS-CoV-2 D614G variant will be measured with the neutralization assay • Antibody titer at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202

[redacted]

Objectives	Endpoints
	(Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Fold-rise (fold-rise in serum neutralization titer post-vaccination relative to D01) at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • 2-fold and 4-fold-rise in serum neutralization titer (post/pre) relative to D01 at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2) • Occurrence of neutralizing antibody seroconversion, defined as values below LLOQ at D91 (Cohort 1) or D112 (Sentinel Cohort and Cohort 2), baseline with detectable neutralization titer above assay LLOQ at D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2)
Efficacy 1) To describe the occurrence of virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection. 2) To evaluate the correlation/association between antibody responses to SARS-CoV-2 mRNA vaccine and the risk of virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection.	***Efficacy*** • Virologically-confirmed COVID-19-like illness as defined by specified clinical symptoms and signs and confirmed by a positive result for SARS-CoV-2 nucleic acid viral detection assay • Serologically-confirmed SARS-CoV-2 infection as defined by SARS-CoV-2 Nucleoprotein specific antibody detection immunoassay • Correlates of risk/protection based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization or ELISA, considering virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection as defined above

[redacted]

Objectives	Endpoints
Exploratory	
Immunogenicity 1) To assess the T-cell cytokine profile at D01, D22 and D36 in the AIT subset. 2) To further assess the cellular immune response at D01, D22, D36, and D112 in the AIT subset. 3) To describe the ratio between neutralizing antibodies and binding antibodies. 4) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains at each pre-defined time point of each study intervention group.	***Immunogenicity*** • T-helper cell (Th1) and Th2 cytokines measured in whole blood following stimulation with full-length S protein at D01, D22 and D36 • T cell responses measured in PBMCs following stimulation with full-length S protein and pools of S antigen peptides by intracellular cytokine staining at D01, D22 and D36 • Spike–Specific IgG/IgA Memory B Cells measured by FluoroSpot assay in peripheral blood mononuclear cells after polycloncal stimulation before vaccination (D01) and at 3-month after second vaccination (D112) • Ratio between binding antibody (ELISA) concentration and neutralizing antibody titer Neutralizing antibody titers against the SARS-CoV-2 variant strains will be measured with the neutralization assay • Antibody titer at each pre-defined time point • Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer (post/pre) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with detectable neutralization titer above assay LLOQ at each pre-defined post-vaccination timepoint and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint
Other To evaluate other emerging biomarkers for immune profiling (further characterization of humoral and/or cellular responses which may include cell profiling), as effect modifiers (may include viral characterization) or as correlates of risk/protection.	Biomarker measurement at baseline, respiratory samples, and/or post-vaccination visits (D22, D36, D91 [Cohort 1] or D112 [Sentinel Cohort and Cohort 2], D181 [Cohort 1] or D202 [Sentinel Cohort and Cohort 2]), and D366 (Cohort 1) or D387 (Sentinel Cohort and Cohort 2)

[redacted]

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Phase I/II, first-in-human, multi-center, safety and immunogenicity study comprised of 2 sequential cohorts: • Lead-in, open-label, Sentinel Cohort (initial target of 25 participants) with Complete Sentinel Early Safety Data Reviews (CS-ESDRs) In case an alert threshold is met in a dose-level group, the Sentinel Cohort for the corresponding dose-level group could be expanded to reach a total of approximately 25 participants (Table 1.1). • Randomized, modified double-blind, placebo-controlled Full Enrollment Cohort (initial target of 308 participants, but actual number could be lower as it will be determined by dose-levels progressing after CS-ESDR). Includes Cohort 1 and Cohort 2 (Table 1.2).
Phase	I/II
Control method	• Open-label, without placebo group for Sentinel Cohort • Placebo-controlled for Full Enrollment Cohort
Study population	Healthy, adults 18 years of age and older without prior serologic evidence of SARS-CoV-2 infection
Level and method of blinding	*For Sentinel Cohort* • Open-label without blinding of participants, site Investigators and staff, and Sponsor • No blinding for injection schedule as all participants will receive 2 vaccinations *For Full Enrollment Cohort* • Blinding for vaccine group assignment (formulation): participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff • No blinding for injection schedule

[redacted]

	• Only study site staff who prepare and administer the vaccine and are not involved with the safety evaluations will be unblinded to study intervention assignment
Study intervention assignment method	The entire study population will be comprised of 2 sequential cohorts: the Sentinel Cohort and the Full Enrollment Cohort. • Sentinel Cohort: participants will be 18-49 years of age and will be assigned to receive 2 injections of one of the 3 dose-levels of the study vaccine, 21 days apart, enrolled in an open-label, dose-escalation manner. The Sentinel Cohort is comprised of the Initial Sentinel Cohorts for the [redacted] µg and the [redacted] µg dose-levels and the Expanded Sentinel Cohort for the [redacted] µg (Figure 1.5). As the study progresses, further addition of participants can occur from the [redacted] µg Initial Sentinel participants and/or possibly the [redacted] µg and [redacted] µg Expanded Sentinel Cohorts. • Full Enrollment Cohort: participants will be 18 years of age and above and will be randomized to receive either 1 injection (Cohort 1) or 2 injections, 21 days apart (Cohort 2), of one of the 3 dose-levels of the study vaccine or placebo. The Full Enrollment Cohort will be stratified by age: targeting a total of up to 140 participants in the 18 through 49 years and up to 168 participants in the ≥ 50 years age groups.
Number of participants	• a target of 25 participants in the Initial Sentinel Cohort (if the [redacted] µg dose escalation is reached) and 20 participants in the Expanded Sentinel Cohort for the [redacted] µg dose-level; additional participants if other dose-level groups of the Sentinel Cohort are expanded; • a target of 308 participants in the Full Enrollment Cohort (if all doses progress); • 5 participants 18 through 49 years of age have already been enrolled in the Initial Sentinel Cohort for the low-dose group.
Intervention groups	Sentinel Cohort: participants will be assigned to one of the 3 groups to receive the ultra-low-dose ([redacted] µg), low-dose ([redacted] µg), or medium-dose ([redacted] µg). Participants in this cohort will be dosed in a stepwise open-label manner. Full Enrollment Cohort: within each cohort (ie, Cohort 1 and Cohort 2), participants will be randomized to up to 4 groups

[redacted]

	to receive the ultra-low-dose ([redacted] µg), low-dose ([redacted] µg), medium-dose ([redacted] µg), or placebo. The ratio for each active arm selected for progression into the Full Enrollment Cohort versus placebo will be 2:1 (ie, ratio of 2:2:2:1 if all dose levels advance into the Full Enrollment Cohort). See also Table 4.2 and Table 4.3 below.
Total duration of study participation	Approximately 365 days post-last dose: • All Sentinel Cohort participants: approximately 386 days duration total • Cohort 1 of Full Enrollment Cohort: approximately 365 days duration total • Cohort 2 of Full Enrollment Cohort: approximately 386 days duration total
Countries	United States, Honduras
Use of an Independent Data Monitoring Committee, Dose-Escalation Committee, or similar review group	No

Modification of Study Design Following the Protocol Amendment

In the original protocol, the first 15 participants to receive the SARS-CoV-2 mRNA vaccine were to be enrolled in a Safety Sentinel Cohort. These participants were to receive 2 injections of the study intervention, 21 days apart, in an open-label, dose-escalation manner. Five participants were to be enrolled in each of the 3 dose-level groups [redacted] as shown in Figure 1.4.

As planned in the original protocol, 5 participants were assigned to the low-dose-level of [redacted] µg, received their first injection, and were contacted by telephone on D03 to document local and systemic solicited reactions as well as unsolicited adverse events (AEs). [redacted]

- The 5 participants in the low-dose ([redacted] µg) group continued their participation in the study. Following the review of the D01-D09 safety and reactogenicity data, the SMT decided that administration of the second study intervention 21 days after the first one could proceed as planned in the original protocol.

[redacted]

- As per this protocol amendment, the ultra-low-dose ([redacted] µg) group will be introduced. The 10 participants in this new Sentinel Cohort group will receive their first vaccination and will be contacted by telephone on D03 to document local and systemic solicited reactions as well as unsolicited AEs during this period in the CRF.
- Also, concurrent with the initiation of the [redacted] µg Initial Sentinel Cohort, as per this protocol amendment, the Expanded Sentinel Cohort for the [redacted] µg dose will enroll an additional 20 participants to better understand the reactogenicity at this dose-level in a larger group of participants.

The progression of the Initial and possible Expanded Sentinel Cohorts are displayed in Figure 1.1.

The Expanded Sentinel Cohort participants in the [redacted] µg dose-level will be contacted by telephone on D03 post-vaccination to document local and systemic solicited reactions as well as unsolicited AEs during this period. Based on the assessment of alert thresholds and other safety parameters for the [redacted] µg dose Expanded Sentinel Cohort, the SMT will determine whether or not the 10 Initial Sentinel Cohort participants for the medium-dose-level of [redacted] µg will be vaccinated.

In addition, ad hoc SMTs for any Sentinel Cohort group may occur to evaluate D01-D09 additional safety data, including laboratory data as needed, to better understand safety. Such ad hoc SMT evaluations will inform study progression, especially if any Sentinel Cohort groups reach the time of second vaccination before CS-ESDR-1 takes place.

For the [redacted] µg and [redacted] µg dose-level groups, an Expanded Sentinel Cohort may be triggered if an alert threshold (see list of threshold in Section 8.4.1) is met in the context of no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the product at a given dose-level prior to triggering study progression decisions (within the same dose-level arm, or in relation to progression to other dose-levels). In case, the Expanded Sentinel Cohort for the ultra-low-dose is triggered, it may run concurrently with the medium-dose Initial or Expanded Sentinel Cohort groups (Figure 1.5). It is to be noted that, if vaccination in the ultra-low- and medium-dose Sentinel Cohort groups do not run concurrently, the possible triggering of an Expanded Sentinel Cohort for the ultra-low-dose group will not impact enrollment in the medium-dose group.

Intervention Groups

The Initial Sentinel Cohort participants will be 18 through 49 years of age and will be assigned to receive 2 injections of the study intervention, 21 days apart, in an open-label manner. Clinical safety laboratory evaluations will be performed at screening and 8 days after each injection. The 5 participants in the low-dose group have already been enrolled. The total number of participants to be enrolled in the Sentinel Cohort, including possibly expanded dose-level groups, is shown in Table 4.2.

[redacted]

Table 4.2: Planned sample size (Sentinel Cohort; 18 through 49 years)

Cohort	Group	Dose-level*	Initial Sentinel Cohort N	Expanded Sentinel Cohort† N	Total Sentinel Cohort
Sentinel Cohort: 2 injections	**1**	[redacted] µg	10	15	25
	2	[redacted] µg	5	20	25
	3	[redacted] µg	10	15	25

* Formulation: SARS-CoV-2 mRNA: ultra-low-dose ([redacted] µg); low-dose ([redacted] µg); medium-dose ([redacted] µg).

† The Expanded Sentinel Cohort for a corresponding dose-level may be triggered only after careful assessment of the Initial Sentinel Cohort for the frequency, severity, and duration of adverse events and proceed if there are no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the vaccine at a given dose-level prior to triggering study progression decisions.

The Full Enrollment Cohort includes both Cohort 1 and Cohort 2. Participants in Cohort 1 of the Full Enrollment Cohort (hereafter referred to as Cohort 1) will receive a single injection of study intervention while participants in Cohort 2 of the Full Enrollment Cohort (hereafter referred to as Cohort 2) will receive 2 vaccinations (to be given 21 days apart), of one of the study interventions (ultra-low-dose [[redacted] µg], low-dose [[redacted] µg], medium-dose [[redacted] µg] or placebo) at D01 (VAC1). The Full Enrollment Cohort planned sample size, assuming all dose-levels progress to full enrollment, is presented in Table 4.3.

Table 4.3: Full Enrollment Cohort - planned sample size

Cohort	Group	Dose-level*	N		Total
			18-49 years	≥ 50 years	
Cohort 1: 1 injection	**1**	[redacted] µg	20	24	44
	2	[redacted] µg	20	24	44
	3	[redacted] µg	20	24	44
	4	Placebo	10	12	22
Cohort 2: 2 injections	**5**	[redacted] µg	20	24	44
	6	[redacted] µg	20	24	44
	7	[redacted] µg	20	24	44
	8	Placebo	10	12	22

* Formulation: SARS-CoV-2 mRNA: ultra-low-dose ([redacted] µg); low-dose ([redacted] µg); medium-dose ([redacted] µg).

Note: A subset of up to 77 randomly selected participants in Cohort 2 (approximately 50% of participants in each of Groups 5 to 8, under 18-49 years and ≥ 50 years age sub-groups) will be included in an Additional Immunological Tests (AIT) subset.

[redacted]

Study Design

Sentinel Cohorts

Participants in the Sentinel Cohort will receive the first injection of the study intervention (ultra-low-dose [µg], low-dose [µg], or medium-dose [µg] at D01 (Vaccination [VAC] 1) in a staged fashion. Refer to Figure 1.5 for the graphical design of the Sentinel Cohort.

Participants from the Sentinel Cohort will receive their second vaccination (VAC2), 21 days after VAC1, if deemed appropriate after SMT data review of safety and reactogenicity data post VAC1. Participants in each the ultra-low-, low-, and medium-dose groups will receive their second vaccination in the same fashion as the first vaccination with intervening SMTs assessing early reactogenicity. Participants will be contacted by phone on D03 to collect D01-03 safety data and SMT evaluation for each group of Sentinel participants.

Complete Sentinel ESDR and Full Enrollment Cohort

The first CS-ESDR (ie, CS-ESDR-1) will be performed for all Sentinel Cohort participants after safety data, including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, is obtained from D01-D09 following the first injection. This unblinded review will be performed by the Sponsor during the SMT meetings. Details of the planned safety parameters and alert thresholds to be examined for the Sentinel Cohort CS-ESDR safety analysis are provided in Section 8.4.2. Progression to the Full Enrollment Cohort for selected or all of the dose levels will occur after CS-ESDR-1 with evaluation of safety data up to D09 post first vaccination in all Sentinel Cohorts participants.

If no safety signals or major tolerability concerns are identified at CS-ESDR-1, the double-blind enrollment of up to 308 participants (vaccine and placebo groups) for the first vaccination of the Full Enrollment Cohort (Cohort 1 allocated to the single-injection schedule and Cohort 2 allocated to the 2-injection schedule) will be initiated. It is to be noted that the first vaccination in the Full Enrollment Cohort may be delayed until after the second vaccination of some of the Sentinel Cohort groups or even postponed until after CS-ESDR-2, if deemed necessary by the SMT.

After CS ESDR-1, participants in Cohort 1 will receive their injection of study intervention while participants in Cohort 2 will receive the first of 2 injections of the study intervention at D01 (VAC1).

A subsequent safety review (CS-ESDR-2) is planned for all Sentinel Cohort participants during which the unblinded SMT will examine the available D22-D30 safety data post-second vaccination including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, and all available MAAEs, SAEs, and AESIs for the Sentinel Cohort participants will also be reviewed. If no safety signals or major tolerability concerns are identified during this period in the Sentinel Cohort, then all participants in Cohort 2 will progress to get the second injection (VAC2). If a safety signal or a major tolerability concern is identified at CS-ESDR-2 for the Sentinel Cohort, then Cohort 2 participants for the corresponding dose-level may not receive their second vaccination.

It should be noted that throughout the study, the SMT core members, consisting of Clinical Team Leader (Responsible Medical Officer [RMO]), Study Biostatistician, Pharmacovigilance Science Expert, and Global Safety Officer, will continuously review blinded safety data, except for the

safety reviews for the Sentinel Cohort and the planned interim analyses, during which unblinded safety data will be reviewed. Further unblinding may be necessary if any of the halting rules are met (see Section 8.4.3) or if there is any safety concern.

Participants follow-up

Participants will be followed over the duration of the study for development of symptoms of COVID-19-like illness. Participants will receive surveillance phone calls every 2 weeks (± 6 days starting after the D43 contact to approximately 6 months) or may be contacted through alternative contact methods (text messages, email, and/or home visit) to enquire about the development of symptoms of COVID-19-like illness and to remind the participants to contact study staff if they experience symptoms of COVID-19-like illness. In addition, all participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study. The reporting of events temporally associated with COVID-19-like illness are outlined in Table 1.6.

Authorized for emergency use and Approved SARS-CoV-2 vaccines

If an approved/authorized SARS-CoV-2 vaccine is available in the country or region where the study is conducted, investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized SARS-CoV-2 vaccine if applicable to them. Recruitment and enrollment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at least until completion of the key follow-up timepoint (D43) of this study for informing progression to further clinical development and dose selection.

If the participant is enrolled and seeks vaccination of an authorized/approved 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 any time. If the participant receives the authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved COVID-19 vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants will be invited to a visit prior to receiving the vaccine and requested to provide a blood sample for immunological assessment. Participants will not receive the second vaccination if they have received the authorized/approved COVID-19 vaccine between the first and second scheduled vaccination.

4.2 Scientific Rationale for Study Design

Rationale for Development Approach

Sanofi Pasteur's development of the SARS-CoV-2 mRNA vaccine candidate is taking place in the setting of a pandemic. At present, 2 COVID-19 mRNA vaccines and 1 viral vector vaccine have received authorization for emergency use in the US and in several countries; however, there is still a need for more vaccines to meet the global demand. As such, the emphasis of the development plan is to rapidly generate data required to support approval and vaccine deployment in the field. This setting mandates consideration of reasonable measures to accelerate development. This

[redacted]

first-in-human study proposes several elements to speed up clinical evaluation and are integrated into the study design while providing required data for the adequate assessment of the immune response profile and safety of the candidate vaccine through efficacy evaluation.

Most current Sponsors of clinical studies for COVID-19 vaccines have accelerated the clinical development of mRNA vaccines based on preclinical safety and toxicological studies for their platform LNP complexed with mRNA encoding antigens from other pathogens (different than SARS-CoV-2) and not based on specific studies for the SARS-CoV-2/lipid combination. In early development, the safety and immunogenicity of the LNP [redacted] was initially tested at Sanofi Pasteur in both mouse and NHP models using mRNA encoding influenza hemagglutinin (HA) where it was found to be well tolerated and induced potent HA neutralizing antibodies in the range of doses selected for this study. Subsequently, a repeated dose nonclinical toxicology study in New Zealand White rabbits with the SARS-CoV-2 mRNA vaccine candidate showed that 3 IM injections of the SARS-CoV-2 mRNA vaccine at 3 weeks interval, up to the dose level of [redacted] µg mRNA/injection were locally and systemically well tolerated (data are summarized in the IB). In preclinical studies, SARS-CoV-2 mRNA vaccine induced dose-dependent S-specific binding and neutralizing antibody response with Th1-biased cellular responses in the mouse model. In the NHP model, the SARS-CoV-2 mRNA vaccine induced dose-dependent S-specific binding and neutralizing antibody response at doses as low as [redacted] µg. Th1-biased cellular responses were observed for the [redacted] µg, [redacted] µg, and [redacted] µg (not assessed at the [redacted] µg dose in NHP). Moreover, hamster challenge studies, designed to assess the protective efficacy of the SARS CoV-2 mRNA Vaccine against viral infection and disease, demonstrated that both single- or 2-dose intramuscular administration at clinically relevant dose levels protected against COVID-19 disease, as measured by the complete prevention of challenge virus induced weight loss and prevention of lung infection in vaccinated hamster (refer to the Investigator's Brochure [IB] for details). Additional nonclinical safety evaluations will proceed in parallel to the Phase III clinical study.

This first-in-human study (VAW00001) design will target an Initial Sentinel Cohort of up to 25 participants (younger adults only). The option of an Expanded Sentinel Cohort for a corresponding dose-level may be triggered if there are no major safety concerns and the SMT judges that further data is needed to cautiously characterize the safety and reactogenicity of the vaccine at a given dose-level prior to triggering study progression decisions (within the same dose-level arm, or in relation to progression to other dose-levels); [redacted] A CS-ESDR will be performed, including evaluation of safety data through D08 and laboratory measures on D09. Upon acceptable safety demonstrated from unblinded review by the SMT with limited members of the Sponsor Study Team (RMO, Biostatistician and Programmer, Pharmacovigilance Science Expert, and Global Safety Officer), the participants in Cohort 1 and Cohort 2 will be enrolled.

The goal of VAW00001 study will be to select a dose and a vaccination schedule to proceed for further clinical evaluation as rapidly as possible. Data up to D43, in addition to preclinical data, will support the selection of a dose and schedule to proceed to further clinical development. The longer term objective is to longitudinally define the safety and durability of the immune response induced by the SARS-CoV-2 mRNA vaccine over the 1 year study duration.

The key readouts informing the decisions to be applied in future clinical development will include data for all participants, who received the 1- or 2-injection schedules. Participants will belong to

[redacted]

either the younger (18-49 years of age) or the older (50 years of age and above) age stratum. The critical data includes the data through D43 post-last vaccination for all participants, including participants enrolled in the Sentinel Cohort, and covers:

a) Safety: immediate AEs, local and systemic reactogenicity through D08, biological safety parameters on D09 post each injection, unsolicited AEs, MAAEs, AESIs, and SAEs through D21 post each injection

b) Neutralizing antibody and binding antibody profiles at D01, D22, and D36

c) Measurement of Th1 and Th2 cytokines in whole blood following stimulation with full-length S protein at D01, D22, and D36 in a randomized subset of Cohort 2 participants

The criteria utilized to define progression to further clinical development will include the above clinical data but will also take into account nonclinical safety, immunogenicity, and efficacy (after virus challenge) data.

Given the important public health need, initial intended use of the SARS-CoV-2 mRNA vaccine is for adults, 18 years of age and older. It is planned that studies to support use of the vaccine in children 6 months to 17 years of age will be conducted after the initial data from studies in adults are available.

Rationale for Injection Schedule

This Phase I/II study will evaluate 2 different vaccination schedules: 1 vaccination or 2 vaccinations, given 21 days apart. In the setting of a pandemic, a single injection would be ideal to be able to protect vaccinees as early as possible. However, given the lack of pre-existing immune responses to SARS-CoV-2, it is possible that 2 injections will be necessary.

A separation of 21 days for the 2-injection schedule is proposed for this program, mirroring the schedule that was evaluated and approved for pandemic influenza vaccines to address the 2009 H1N1 influenza pandemic (AS03 adjuvanted vaccines Pandemrix™, Arepanrix™; and AF03 adjuvanted Humenza vaccine). This schedule results in a second injection of the vaccine being administered earlier than with other common vaccines with longer separations between injections (ie, 28 days), thus aiming at earlier generation of potentially protective immune responses. This may be of particular interest in an ongoing pandemic setting and is also supported by the preclinical studies for the SARS CoV-2 mRNA vaccine.

In addition to antibody response 21 days after injection, durability after a single injection also needs to be taken into account for schedule selection, as peak immune responses after 1 injection may be adequate but could (at least theoretically) wane rapidly, potentially leaving vaccinees at risk in the event of ongoing circulation of novel coronavirus. Therefore, antibody titers at D22 (21 days after the first vaccination) and D36 (14 days after the second vaccination) after 1 or after 2 injections are considered relevant for informing schedule selection.

Rationale for Study Arms

Participants in the Sentinel Cohort will receive injections of the study intervention (ultra-low-dose [[redacted] µg], low-dose [[redacted] µg], or medium-dose [[redacted] µg]) at D01 (VAC1) and D22 (VAC2) in a staged fashion. Participants in Cohort 1 and Cohort 2 are planned to receive 1 injection of the study

[redacted]

intervention (ultra-low-dose [[redacted] µg], low-dose [[redacted] µg], medium-dose [[redacted] µg], or placebo) at D01 (VAC1). Participants in Cohort 2 of the Full Enrollment Cohort will receive a second vaccination of study intervention (same study intervention as received at D01) at D22 (VAC2). Comparisons between Cohort 1 and Cohort 2 will inform decisions on schedule selection. Comparison between dose-levels for safety and immunogenicity will inform decisions on dose selection for the Phase III study. The placebo arm in the Full Enrollment Cohort allows for blinding and also provides background information for safety assessments.

Rationale for Immunogenicity Objectives and Endpoints

The primary immunogenicity endpoint, based on neutralizing antibodies, is expected to provide the most relevant evaluation of functional immune responses for this vaccine candidate, supported by controlled human infection studies that have identified the presence of pre-challenge neutralizing antibodies as predictive of protection from coronavirus infection or symptoms following challenge (26) (27).

This study will also include exploratory immunogenicity objectives to further describe the immune response, including T cell and memory B cell responses at D01, D22, D36, and D112 for each study intervention group in a subset of up to 77 participants. Based on the preclinical studies undertaken with prior SARS vaccine candidates, and the possible immunopathologic mechanisms identified in these studies, the Sponsor proposes to evaluate cytokine secretion associated with a Th1 and Th2 T-cell profile generated following vaccination. To balance operational considerations and to improve the interpretability of cell-mediated immunity (CMI) data given the limited experience with CMI measurements for this pathogen, a longitudinal sampling strategy was prioritized over increasing sample collection at a single post-vaccination time-point. Thus, CMI studies will be performed in a subset of randomized participants in Cohort 2 of the Full Enrollment Cohort, with samples obtained at baseline, and following first and second injection. In addition, to characterize the relative induction of functional to total antibody responses generated following vaccination, the ratio between neutralizing antibodies and binding antibodies will be described. Given the emerging knowledge about SARS-CoV-2 evolution and variants prevalence across the globe, exploratory endpoints will include the evaluation of immune responses directed towards relevant viral variants.

Rationale for Study Population

The study will enroll participants with no history of COVID-19 and no serologic evidence of SARS-CoV-2 infection by rapid diagnostic test at the screening visit. Inclusion of individuals with prior exposure to SARS-CoV-2 would be expected to influence immunogenicity measures. The aim of this study is to identify the dose-level of SARS-CoV-2 mRNA vaccine formulation that best supports an immune response in the naïve population, considered the population most at need for a preventive solution against SARS-CoV-2. While protection against reinfection after natural infection is not yet clearly demonstrated, data from human challenge models with other coronaviruses suggests at least short to midterm protection (28) (26). In addition, studies in NHPs indicate that animals infected with SARS-CoV-2 are protected against reinfection at least in the short term (29). While there are reports of previously infected individuals that re-test positive to SARS-CoV-2, it is not clear at present whether this is the result of sampling or testing limitations (intermittent false negativity), reactivation of the virus, or reinfection. Preliminary data also

[redacted]

indicate that in the majority of instances where this has been reported, individuals are asymptomatic or have milder symptoms. Taken together, all this information suggests that SARS-CoV-2 seropositive individuals may be protected from reinfection, and if reinfection or recurrence occurs, the burden of illness is likely to be smaller and potentially associated with lesser impact on public health compared to that of seronegative persons. Therefore, the immunogenicity and safety data in this study are targeted to be generated in individuals without evidence of prior exposure to SARS-CoV-2 infection.

In this study, we plan to enroll adults 18 years of age and older. Clinical and epidemiological data from the COVID-19 pandemic have consistently indicated a higher burden of disease with higher risk of severe complications and death in older adults (30). Because of this, we believe including older adults in the study is of great relevance to generate data to inform schedule selection that will serve the general adult population.

Clinical and epidemiological data also indicate that advanced age and those with chronic medical conditions are at increased risk of severe outcomes associated with COVID-19. The excess mortality from COVID-19 illness in the elderly may also be compounded by the higher prevalence of comorbidities in this age group (31) (32). Exclusion of individuals with chronic medical conditions from this study mitigates the potential risk of exacerbating poor outcomes as a result of study participation. The exclusion of individuals with chronic underlying conditions is also considered a risk mitigation measure to address the theoretical phenomenon of immune enhancement in this study population (17).

Another risk mitigation strategy is to restrict enrollment for the Sentinel Cohort to younger adults 18 through 49 years of age. After performing CS-ESDR-1 and if no safety signals or major tolerability concerns are identified in this cohort of younger participants, full enrollment will be opened to all younger and older age groups simultaneously. The simultaneous enrollment based on the inclusion of healthy older adults, at higher risk for severe outcomes and without evidence of previous SARS-CoV-2 infection is warranted and will prevent a delay in the program and allow rapid data generation to support further clinical development.

No upper age range is specified as long as other inclusion/exclusion criteria are met. Complete exclusion of older individuals from the study would compromise the timely progression of the clinical development plan and the deployment of the vaccine to the field (if a sequential enrollment of older adults was required), or result in selection of a formulation without knowledge about immunogenicity and safety patterns in older adults (if program progression was only informed by data from younger adults).

Furthermore, the Full Enrollment Cohort proposes a relatively balanced representation of the younger and older adult strata (ie, up to 140 in younger adults; and up to 168 in older adults; with younger adult data further informed by data generated in the Sentinel Cohorts). Data for each dose will be generated in both younger adults and older adults, allowing the evaluation of the consistency in the patterns of immune response for each dose between the 2 age strata; additionally, aggregated “main” effects by age will be evaluable by comparing pooled older adult data (enrollment target of approximately 144 participants across vaccine dose-levels) and pooled younger adult data (enrollment target of approximately 145 participants across vaccine dose-levels).

[redacted]

Rationale for Blinding

In the Sentinel Cohort there will be no blinding. However, the Full Enrollment Cohort will be double-blind for study intervention (SARS-CoV-2 mRNA vaccine and placebo). Owing to the need for mixing of study formulation and diluent to prepare the vaccine, the person preparing and administering the study intervention will be unblinded to study intervention assignment. Blinding of all other people will minimize the risk of bias arising from the possibility of consciously or unconsciously influencing the reporting of study outcome measures and knowledge of the formulation administered.

Rationale for Placebo in Full Enrollment Cohort

Placebo, rather than a benefit licensed vaccine, will be used for comparison to vaccine to allow safety comparisons between vaccine and placebo as currently emergency use authorized COVID-19 vaccines are not widely available. The number in the placebo group have been decreased to expose fewer participants to placebo. The inclusion of placebo group will also maintain the blind, allowing the unbiased evaluation of safety, immunogenicity, and clinical outcomes related to COVID-19-like illness and SARS-CoV-2 infection by treatment group.

Rationale for Staged Enrollment of Study Intervention Groups in Sentinel Cohort

The proposed Sentinel Cohort will enroll 10 participants for the ultra-low-dose (µg) group, 5 participants for the low-dose group (µg), and 10 participants for the medium-dose (µg) group. All 3 arms can possibly be expanded to a total of approximately 25 participants per dose-level group in case further data is needed to cautiously characterize the safety and reactogenicity of the product at a given dose-level. The Expansion of the Sentinel Cohort and expansion of the ultra-low- or/and medium-dose levels remain as optional. Following amendment of the protocol, the Sentinel Cohort will still be enrolled in a dose-escalation manner (for the medium-dose arm) as opposed to in a simultaneous fashion. It is generally expected that reactogenicity to vaccine candidates will be higher with higher antigen doses. As neither the vaccine candidates nor the LNP utilized in this study have been administered to humans before, a cautious sequential approach is advised to allow close monitoring of safety/reactogenicity parameters to inform progression from low to higher doses.

4.3 Justification for Dose

The selection of the lower-dose formulation for this study is based on the safety and immunogenicity from nonclinical studies, on data generated with other mRNA vaccines in nonclinical and human studies. Following the safety and reactogenicity data obtained in the 5 participants in the low-dose group of the Sentinel Cohort, the dose-level range the Sponsor originally intended to evaluate was lowered (ie, ultra-low-, low-, and medium-dose-levels).

Nonclinical Dose Ranging Safety Studies (nonclinical toxicology) of the LNP with an influenza mRNA antigen identified the no-observed-adverse-effect level (NOAEL) at µg . Initial entry doses selected for this study (µg, µg, and µg) were all below this NOAEL and were further supported by a Good Laboratory

Practice toxicology study. Information gathered based on the experience of other mRNA vaccine candidates were also supportive of this dose range. Nonclinical studies performed at Sanofi Pasteur in collaboration with Translate Bio have indicated [redacted] has been utilized as the LNP in studies evaluating pandemic influenza vaccine candidates (33) that showed robust immune responses with doses of 25-50 µg of mRNA. In addition, data with another mRNA SARS-CoV-2 vaccine candidate suggested antibody responses similar or higher to those observed in convalescent sera with mRNA dose-levels of 25 µg and 100 µg and responses greater for individuals receiving the 100 µg dose; they also reported high frequency of Grade 3 systemic reactogenicity with a dose-level of 250 µg of mRNA (34). The other mRNA vaccine candidate was tested at 2 dose-levels (50 µg and 100 µg) in a Phase II study, and a 100 µg dose progressed to a Phase III study and is currently under emergency use authorization (EUA).

[redacted]

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 Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of the last contact 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.

[redacted]

5.1 Inclusion Criteria

5.1.1 Inclusion Criteria to be Checked at Screening Visit

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

I01: Aged ≥ 18 years[a] on the day of inclusion

I02: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal 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 the first vaccination until at least 12 weeks after the last vaccination.

A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 8 hours before the study intervention, see Section 8.4.8 Pregnancy testing.

I03: Informed Consent Form (ICF) has been signed and dated

I04: Able to attend all scheduled visits and to comply with all study procedures

I05: Participant not eligible to receive, based on local guidance, or if eligible does not intend to receive an authorized/approved COVID-19 vaccine from first vaccination until completion of the key timepoint of D43 of follow-up of this study[b]

5.1.2 Inclusion Criteria to be Checked at Visit 1

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

I01: Aged ≥ 18 years[c] on the day of inclusion

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[a] "≥ 18 years" means from the day of the 18th birthday onwards, with no upper age limit.

[b] While recruitment of eligible participants will proceed only if the candidate participant expresses no intention to seek an authorized or approved vaccine until completion of the key follow-up timepoint (D43), if the participant is enrolled and seeks vaccination of an authorized/approved COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the trial investigator and will be permitted to receive the authorized vaccine at any time. If the participant receives the authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved COVID-19 vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to be followed for the duration of the trial as per scheduled visits and procedures. Participants will not receive the second vaccination if they have received the authorized/approved COVID-19 vaccine between the first and second scheduled vaccination (see Section 7.1.2 : Definitive Contraindications).

[c] "≥ 18 years" means from the day of the 18th birthday onwards, with no upper age limit.

[redacted]

I02: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal 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 the first vaccination until at least 12 weeks after the last vaccination.

A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 8 hours before the study intervention, see Section 8.4.8 Pregnancy testing.

I04: Able to attend all scheduled visits and to comply with all study procedures

I05: Participant not eligible to receive, based on local guidance, or if eligible does not intend to receive an authorized/approved COVID-19 vaccine from first vaccination until completion of the key timepoint of D43 of follow-up of this study[a]

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria to be Checked at Screening Visit

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

E01: History of COVID-19 disease or prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed serologically

E02: Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure

E03: Prior administration of a coronavirus vaccine (SARS-CoV-2, SARS-CoV, Middle East Respiratory Syndrome coronavirus [MERS-CoV])

[a] While recruitment of eligible participants will proceed only if the candidate participant expresses no intention to seek an authorized or approved vaccine until completion of the key follow-up timepoint (D43), if the participant is enrolled and seeks vaccination of an authorized/approved COVID-19 vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the trial investigator and will be permitted to receive the authorized vaccine at any time. If the participant receives the authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved COVID-19 vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to be followed for the duration of the trial as per scheduled visits and procedures. Participants will not receive the second vaccination if they have received the authorized/approved COVID-19 vaccine between the first and second scheduled vaccination (see Section 7.1.2: Definitive Contraindications).

[redacted]

E04: Receipt of any vaccine in the 30 days preceding the first study vaccination or planned receipt of any vaccine in the 30 days following the last study vaccination except for influenza vaccination, which may be received at least 2 weeks before and a minimum of 2 weeks after study vaccines[a]

E05: Receipt of immune-globulins, blood or blood-derived products in the past 3 months

E06: 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)

E07: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances[b]

E08: Self-reported thrombocytopenia, contraindicating intramuscular vaccination based on Investigator's judgment

E09: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination based on Investigator's judgment

E10: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E11: Current alcohol abuse or drug addiction

E12: Chronic illness or condition considered to potentially increase the risk for severe COVID illness[c] (25) or that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[d]

E13: Known liver disease or fatty liver

E14: Residence in a nursing home or long-term care facility

E15: Health care workers providing direct patient care for COVID-19 patients

E16: Participants with active or prior documented autoimmune disorder

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[a] While receipt of any vaccine as listed in this criterion is exclusionary for this study, participants are free to receive another available COVID-19 vaccine. Participants who receive another COVID-19 vaccine outside this study will still be followed for safety until the end of the study, but will be discontinued from study intervention administration thereafter (see Section 7.1.2: Definitive Contraindications).

[b] The components of SARS-CoV-2 mRNA vaccine are listed in Section 6.1 and in the SARS-CoV-2 mRNA Investigator's Brochure.

[c] Factors that may increase the risk of severe COVID illness include: autoimmune disease; cerebrovascular disease; chronic pulmonary disease (including moderate-severe asthma, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, pulmonary fibrosis); current smoking or chronic smoking in the past year; current vaping; diabetes mellitus; cardiovascular disease (including hypertension); chronic renal disease; chronic liver disease; immunocompromised condition; neurologic disorder (including dementia), obesity (body mass index ≥ 30); sickle cell disease; known thalassemia; and Down syndrome.

[d] Chronic illness may include, but is not limited to, psychiatric disorders.

[redacted]

E17: Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E18: Receipt of any therapy known to have in-vitro antiviral activity against SARS-CoV-2 within 72 hours prior to BL00001 blood draw[a] or planned use of such therapy 72 hours prior to BL0002 or BL0003 (study immunogenicity blood draws at D22 and D36)

E19: 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

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 Exclusion Criteria to be Checked at Visit 1

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

E01: History of COVID-19 disease or prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed serologically

E02: Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure

E03: Prior administration of a coronavirus vaccine (SARS-CoV-2, SARS-CoV, Middle East Respiratory Syndrome coronavirus [MERS-CoV])

E04: Receipt of any vaccine in the 30 days preceding the first study vaccination or planned receipt of any vaccine in the 30 days following the last study vaccination except for influenza vaccination, which may be received at least 2 weeks before and a minimum of 2 weeks after study vaccines[b]

E05: Receipt of immune-globulins, blood or blood-derived products in the past 3 months

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[a] Therapy/treatment including, but not limited to, favipiravir, lopinavir/ritonavir, remdesivir, arbidol, chloroquine, hydroxychloroquine, ivermectin.

[b] While receipt of any vaccine as listed in this criterion is exclusionary for this study, participants are free to receive another available COVID-19 vaccine. Participants who receive another COVID-19 vaccine outside this study will still be followed for safety until the end of the study, but will be discontinued from study intervention administration thereafter (see Section 7.1.2: Definitive Contraindications).

[redacted]

E06: 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)

E07: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances[a]

E08: Self-reported thrombocytopenia, contraindicating intramuscular vaccination based on Investigator's judgment

E09: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination based on Investigator's judgment

E10: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E11: Current alcohol abuse or drug addiction

E12: Chronic illness or condition considered to potentially increase the risk for severe COVID illness[b] (25) or that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[c]

E13: Known liver disease or fatty liver

E14: Residence in a nursing home or long-term care facility

E15: Health care workers providing direct patient care for COVID-19 patients

E16: Participants with active or prior documented autoimmune disorder

E17: Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.

E18: Receipt of any therapy known to have in-vitro antiviral activity against SARS-CoV-2 within 72 hours prior to BL00001 blood draw[d] or planned use of such therapy

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[a] The components of SARS-CoV-2 mRNA vaccine are listed in Section 6.1 and in the SARS-CoV-2 mRNA Investigator's Brochure.

[b] Factors that may increase the risk of severe COVID illness include: autoimmune disease; cerebrovascular disease; chronic pulmonary disease (including moderate-severe asthma, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, pulmonary fibrosis); current smoking or chronic smoking in the past year; current vaping; diabetes mellitus; cardiovascular disease (including hypertension); chronic renal disease; chronic liver disease; immunocompromised condition; neurologic disorder (including dementia), obesity (body mass index ≥ 30); sickle cell disease; known thalassemia; and Down syndrome.

[c] Chronic illness may include, but is not limited to, psychiatric disorders.

[d] Therapy/treatment including, but not limited to, favipiravir, lopinavir/ritonavir, remdesivir, arbidol, chloroquine, hydroxychloroquine, ivermectin.

[redacted]

72 hours prior to BL0002 or BL0003 (study immunogenicity blood draws at D22 and D36

E19: 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

E20: Platelet count, renal function tests (serum creatinine), liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, prothrombin time [PT], partial thromboplastin time [PTT] with international normalized ratio [INR]), screening laboratory results that fall into the range of values that are Grade 1 or greater. For the remaining screening laboratory parameters that fall into the range of values that are Grade 2 or greater OR Grade 1 that are deemed clinically significant in the opinion of the Investigator (Grade 1 values for laboratory parameters other than those specified here and deemed not clinically significant may be enrolled at the Investigator's discretion).

E21: Positive test for chronic active Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody, or human immunodeficiency virus (HIV) antibody, either from testing conducted within 4 weeks prior to enrollment or from blood work collected at screening visit

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

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not met, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

[redacted]

6 Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Note: routine vaccines administered outside of study protocol are not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

[redacted]

Table 6.1: Identity of study interventions

Intervention Name	**SARS-CoV-2 mRNA (ultra-low-dose)**	**SARS-CoV-2 mRNA (low-dose)**	**SARS-CoV-2 mRNA (medium-dose)**	**Placebo**
Study Groups	Group 1 (Sentinel Cohort), Groups 1 and 5 (Full Enrollment Cohort)	Group 2 (Sentinel Cohort), Groups 2 and 6 (Full Enrollment Cohort)	Group 3 (Sentinel Cohort), Groups 3 and 7 (Full Enrollment Cohort)	Groups 4 and 8 (Full Enrollment Cohort)
	Refer to Table 4.2 and Table 4.3 for group numbers.			
Use	Experimental	Experimental	Experimental	Placebo - comparator
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	Sterile suspension (white to off-white), single use dose vial diluted with buffer at the study site according to dose preparation protocol			Liquid, in a single-vial presentation
Unit Dose Strengths	Each 0.5 mL dose of study intervention after dilution will contain the following:			• 0.9% normal saline
	• SARS-CoV-2 mRNA, ultra-low-dose ([redacted] µg) • LNP [redacted]	• SARS-CoV-2 mRNA, low-dose ([redacted] µg) • LNP [redacted]	• SARS-CoV-2 mRNA, medium-dose ([redacted] µg) • LNP [redacted]	
	The investigational product 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.			

Intervention Name	**SARS-CoV-2 mRNA (ultra-low-dose)**	**SARS-CoV-2 mRNA (low-dose)**	**SARS-CoV-2 mRNA (medium-dose)**	**Placebo**
Excipients/Diluent	[redacted]			None
Dosage Level	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose
Number of Doses/Dosing Interval	Sentinel Cohort: 2 injections, 21 days apart Cohort 1: 1 injection Cohort 2: 2 injections, 21 days apart			Cohort 1: 1 injection Cohort 2: 2 injections, 21 days apart
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Site of Administration	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	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 detachable label(s) and one fixed label containing the dose number. All will be labeled as required per country requirement.			
Batch Number	To be determined	To be determined	To be determined	To be determined

6.2 Preparation/Handling/Storage/Accountability

The investigational product will be formulated as a single dose of mRNA-LNP complex and will be diluted to the required mRNA dose at the study site using a buffer diluent. The product should be stored at -80°C prior clinical use.

Detailed guidance and information are provided in the Operating Guidelines.

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. 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.
3) The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

For the Sentinel Cohort: On the day of enrollment, participants 18 to 49 years of age only, who meet the eligibility criteria and have signed the Informed Consent Form (ICF), will be assigned to the Sentinel Cohort. In this cohort, initially about 25 participants are targeted to be sequentially assigned to receive one of the 3 dose-levels (10 participants in the ultra-low-dose [µg] group; 5 participants in the low-dose [µg; already dosed before protocol amendment] group; 10 participants in the medium-dose [µg] group as shown in Table 4.2. Participants in this cohort will receive 2 injections of the study intervention separated by 21 days. Additional participants may be sequentially assigned to a particular dose-level if and when the Expanded Cohort for the corresponding lose level is triggered. At the time of this protocol amendment, the Expanded Sentinel Cohort for the low-dose (µg) has been exercised, and enrollment of an additional 20 participants at this dose-level is targeted.

For the Full Enrollment Cohort: On the day of randomization, participants who meet the eligibility criteria and sign the ICF will be stratified by 2 age groups (18-49 years and ≥ 50 years) and then be randomly assigned (1:1) to receive 1 injection (Cohort 1) or 2 injections (Cohort 2) of the SARS-CoV-2 mRNA vaccine or placebo (as shown in Table 4.3). Within each cohort, participants will be randomized to up to 4 groups to receive SARS-CoV-2 mRNA vaccine (ultra-low-dose [µg], low-dose [µg], medium-dose [µg], or placebo. The ratio for each active arm

selected for progression into the Full Enrollment Cohort versus placebo will be 2:1 (ie, ratio of 2:2:2:1 if all dose levels advance into the Full Enrollment Cohort).

A subset of up to 77 randomly selected participants in Cohort 2 (50% of participants in each group in each age strata), will be part of the AIT subset and will have additional blood samples collected at D01, D22, D36, and D112 for further immune response characterization and assessment.

IRT Details for All Participants

Site staff will connect to the IRT at screening visit, enter the identification, security information, and confirm a minimal amount of data in response to IRT prompt. At the screening visit, the IRT will provide the participant number. At V01, the IRT will provide the cohort and dose number assignment and have the site staff confirm it. The full detailed procedures for cohort and dose number allocation are described in the Operating Guidelines. 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). For example, Participant 840000100005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code).

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

6.3.2 Blinding and Code-breaking Procedures

For Sentinel Cohort

- The study is unblinded for the Sentinel Cohort

For Full Enrollment Cohort

- Conducted in a modified double-blind fashion
- Investigators and study staff who conduct the safety assessment and the participant will not know which vaccine is administered in order to decrease the risk of potential bias
- Only the study site staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered
- Testing laboratories will be blinded
- Sponsor study team will be blinded, unless unblinding is necessary if the halting rules are met (see Section 8.4.3) or if there is any safety concern

At the time of the interim analysis (see Section 9.5), unblinding at the group-level will take place to inform Sponsor decision on further clinical development. Individual level code will be maintained by the independent unblinded statistician until the end of the study. In addition to that, Global Clinical Immunology (GCI) and other laboratories undertaking assays for the study will be kept blinded until all test results are released.

[redacted]

The code may be broken in the event of an AE only when the identification of the vaccine 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 delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO 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 CRF is to be completed.

The Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) 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 Sanofi Pasteur 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[a]. 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 trial 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.

The code-breaking procedures are described in the Operating Guidelines.

An unblinded review will be done by the Sponsor at the time of the SMT reviews and CS-ESDRs for the Sentinel Cohort participants only.

A preliminary interim safety and immunogenicity analysis can be performed inclusive of up to D43 data for participants enrolled into the Sentinel Safety Cohorts.

At the time of the key interim analysis, the blind will be broken at the group level for the Sponsor, including data collected up to D43 in both the Sentinel and the Full Enrollment Cohorts that will inform further development decisions, after the first database lock; the SMT will review group blinded data at interim analyses with safety outputs. For the rest of the time, SMT will review blinded data for remainder of the study. During the study, if any of the halting rules are met (see Section 8.4.3) or if there is any safety concern, unblinding may be necessary. The participant level data will be maintained blinded on-site until the end of the study/until the interim Clinical Study Report approval, with study participants, study Investigators and testing laboratories remaining blinded at the individual level for the duration of the study, unless unblinding is required to maintain the safety and welfare of participants.

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

[redacted]

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All vaccinations 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

6.5 Concomitant Therapy

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during study participation.

Documentation in the CRF of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination or stopped prior to enrollment.

Reportable medications/vaccinations will be collected in the CRF from the day of each study vaccination to the end of the solicited and unsolicited follow-up period after each vaccination (for Sentinel Cohort and Cohort 2: up to D43; Cohort 1: up to D22). The exception is influenza and COVID-19 vaccinations, which will be collected throughout the study in all participants. In addition, any medications used for COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal or polyclonal antibodies or plasma) will be collected throughout the study in all participants.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs, systemic steroids/corticosteroids)
- Category 2: medications impacting or that may have an impact on the immune response (eg, hydroxychloroquine, other vaccines, blood products, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, immunoglobulins, anti-proliferative drugs such as deoxyribonucleic acid (DNA) synthesis inhibitor)
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic and ear treatments will not be recorded. Topical analgesics should not be

applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

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 CRF unless the medication(s) received belongs to one of the pre-listed categories. Medications will not be coded.

6.5.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on-site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

In the event that the SARS-CoV-2 mRNA vaccine is demonstrated to be safe and efficacious in future development, the vaccine may be offered to the participants in the VAW00001 study who received either placebo or a different/lower dose of the SARS-CoV-2 mRNA vaccine that was demonstrated to be efficacious in the Phase III study, as soon as possible following completion of the VAW00001 study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Section 7.1.1 and Section 7.1.2 are applicable to the Sentinel Cohort and Cohort 2 only.

These sections are not applicable to Cohort 1 as participants in this cohort are planned to receive only 1 vaccination in the study.

7.1.1 Temporary Contraindications

Should a participant experience 1 of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA (Section 1.3).

TCI01: 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

TCI02: Receipt of any vaccine (other than the study vaccine[s]) in the 21 days preceding the second study vaccination or planned receipt of any vaccine in the 30 days following

[redacted]

the second study vaccination except for influenza vaccination, which may be received at least 2 weeks before and a minimum of 2 weeks after study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience 1 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: SAE assessed as related to the study vaccine following the previous dose of vaccine, based on Investigator's judgment

DCI04: A Grade 3 AE, assessed as related to the first study vaccine, that, in the opinion of the Investigator, may place the participant at unreasonable or significant risk of injury or illness following repeat exposure to study vaccine

DCI05: Symptomatic COVID-19 infection confirmed by NAAT in the period between the first study vaccination (V01) and the day corresponding to the second study vaccination (V03)

DCI06: Receipt of COVID-19 vaccine (other than the study vaccine) or anti-SARS-CoV-2 monoclonal or polyclonal antibody in the period between the first study vaccination (V01) and the day corresponding to the second study vaccination (V03)

If the participant is enrolled and seeks vaccination of an authorized/approved 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 any time. If the participant receives the authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved COVID-19 vaccine will be included in the primary analysis for immunogenicity and safety. Participants will be invited to a visit prior to receiving the vaccine and requested to provide a blood sample for immunological assessment. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures except for receipt of the second vaccination as detailed above.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

[redacted]

- The reason for withdrawal should be clearly documented in the source documents and in the CRF: AE, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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 consent, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of "lost to follow-up".

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and 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 cannot be contacted as planned in the SoA (Section 1.3):

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's source documents.
- Should the participant continue to be unreachable, he/she will be considered discontinued from the study with lost to follow-up as a reason for discontinuation.

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

[redacted]

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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.

Urine, blood, and respiratory 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, including any extra assessments that may be required, is not planned to exceed 405 mL (cumulative total) (see Table 8.1). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

[redacted]

Table 8.1: Blood sampling volume per visit

	Screening**	D01	D09	D22	D30	D36	D91/D112	D181/D202	D366/D387
Vaccination		X		X*					
SARS-CoV-2 antibody screen baseline (1 mL)	X								
Screening serology (HIV Ab, HBsAg, HBcAb, HCV Ab) (~5 mL)*	X								
Safety laboratory assessments (~15 mL at each time-point)									
Hematology†	X		X		X‡				
Biochemistry and other serum tests†	X		X		X‡				
PT and PTT with INR	X		X		X‡				
Antibody assays (30 mL at each time-point)		BL0001		BL0002		BL0003	BL0004	BL0005	BL0006
SARS-CoV-2 Neutralization assay		X		X		X	X	X	X
Anti-Spike protein IgG ELISA		X		X		X	X	X	X
SARS-CoV-2 Nucleoprotein specific antibody detection immunoassay		X		X		X	X	X	X
SARS-CoV-2 specific adaptive immune responses (44 mL [4ml for WB and 40 mL for MC samples] at each time-point)§		MC0001 WB0001		MC0002 WB0002		MC0003 WB0003	MC0004		

Abbreviations: BL, blood sample (#);ELISA, enzyme-linked immunosorbent assay; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCVAb, Hepatitis C virus antibody; HIV, human immunodeficiency virus; IgG, immunoglobulin G; INR, international normalized ratio; MC, mononuclear cell; PT, prothrombin time; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WB, whole blood.

* Results for these serology tests obtained within 4 weeks prior to V01 will be accepted.

† Hematology, biochemistry, other serum tests, and urine testing are listed in Table 10.1.

‡ Only for Sentinel Cohort and Cohort 2.

§ Only for randomly chosen participants in the AIT subset of Cohort 2 in Full Enrollment Cohort. Memory B Cell quantification will be performed on MC0001 and MC0004. Intracellular Cytokine Staining will be performed on MC0001, MC0002, and MC0003.

** COVID-19 antibody test and blood and urine sampling for safety tests may be performed on the day of enrollment as long as the results to assess exclusion criteria are available prior to enrollment.

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Baseline Screening for SARS-CoV-2 Antibodies

A blood sample will be obtained before study enrollment to exclude from participation individuals with evidence of SARS-CoV-2 antibodies.

8.2 Immunogenicity and Efficacy Assessments

8.2.1 Immunogenicity Assessments

8.2.1.1 Primary Immunogenicity Assay

SARS-CoV-2 Pseudovirus Neutralization Assay

The SARS-CoV-2 Pseudovirus Neutralization Assay evaluates the level of neutralizing SARS-CoV-2 pseudovirus antibodies present in the human serum samples. Pseudotyped virus particles are made from a modified Vesicular Stomatitis Virus (VSVΔG) backbone and bear the spike glycoprotein of the SARS-CoV-2 from which the last nineteen (19) amino acids of the cytoplasmic tail were removed. The pseudoparticles contain a Luciferase reporter used for detection.

Seven two-fold serial dilutions of heat-inactivated human serum samples are prepared in 96-well transfer plate(s). The SARS-CoV-2 pseudovirus is added sequentially to the serum dilutions at a target working dilution (to obtain approximately 75,000-300,000 RLU/well) and incubated at 37°C with 5% CO2 supplementation for 60 ± 5 minutes. Serum-virus complexes are then transferred onto plates, previously seeded overnight with Vero E6 cells, and incubated at 37°C and with 5% CO2 supplementation for 20 ± 2 hours. Following this incubation, the luciferase substrate is added to the cells in order to assess the level of luminescence per well. The plate(s) are then read on a luminescence plate reader. The intensity of the luminescence is quantified in relative luminescence units (RLU) and is inversely proportional to the level of neutralizing antibodies present in the serum. The neutralizing titer of a serum sample is calculated as the reciprocal serum dilution corresponding to the 50% neutralization antibody titer (NT50) for that sample.

This assay will be used to measure neutralizing antibody responses to the homologous vaccine strain (D614G variant) at all timepoints in all participants. In addition, the assay may be used to measure antibody responses against other emergent variants (eg, B.1.351, B.1.1.7, P.1) for exploratory analyses.

[redacted]

8.2.1.2 Additional Immunogenicity Assays

SARS-CoV-2 Neutralizing Antibody Assessment (SP)

SARS-CoV-2 neutralizing antibodies will be measured using a live virus neutralization assay in all participants at all timepoints and may serve as a supportive assay for the primary endpoint.

Serum samples are mixed with constant concentration of the SARS-CoV-2 virus. A reduction in virus infectivity (viral antigen production) due to neutralization by antibody present in serum samples can be detected by ELISA. After washing and fixation, SARS-CoV-2 antigen production in cells can be detected by successive incubations with an anti-SARS-CoV-2-specific antibody, horseradish peroxide immunoglobulin G conjugate, and a chromogenic substrate. The resulting optical density (OD) is measured using a microplate reader. The reduction in SARS-CoV-2 infectivity as compared to that in the virus control wells constitutes a positive neutralization reaction indicating the presence of neutralizing antibodies in the serum sample.

Serum IgG Antibodies to SARS-CoV-2 Spike Protein Using ELISA

SARS-CoV-2 anti-S protein IgG antibodies will be measured using an ELISA to assess total antibodies to the S protein antigen elicited by the vaccine. Microtiter plates will be coated with SARS-CoV-2 S protein antigen diluted in coating buffer to the optimal concentration.

Plates may be blocked by the addition of a blocking buffer to all wells and incubation for a defined period. Following incubation, plates will be washed. All controls, reference, and samples will be pre-diluted with dilution buffer. The pre-diluted controls, reference and samples will then be further serially diluted in the wells of the coated test plate.

The plates will be incubated for a defined period. Following incubation, plates will be washed, an optimized dilution of goat anti-human IgG enzyme conjugate will be added to all wells, and plates will be further incubated. Following this incubation, the plates will be washed, and enzyme substrate solution will be added to all wells. Plates will be incubated for a defined period to allow the substrate to develop. Substrate development will be stopped by the addition of a stop solution to each well. An ELISA microtiter plate reader will be used to read the test plates using assay specific SoftMax Pro templates.

The average OD value for the plate blank will be subtracted from all the ODs within each plate. The sample titers will be derived using the measured values of the blanks, controls, and the reference standard curve, which will be included on each assay plate within the run.

Additional Immunological Tests

Helper T cell TruCulture

The T cell analysis in the whole blood, collected, using Myraid's TruCulture whole blood collection and culture system, will enable consistent, reliable assessment of the T helper cells polarization. The TruCulture tube containing the stimulant or antigen of choice, allows almost instantaneous stimulation of the cells in the presence of all the blood components, after the blood is drawn into the tube and therefore, minimizes variability that may arise due to the handling and

[redacted]

manipulation of blood, including processing for PBMC. Preliminary results in our laboratories and previous reports in the literature have shown the robustness of the method (35). The assay relies on the fact that the T helper cytokines are secreted in a single tubes post stimulation and supernatant are collected 24 or 48hrs. A panel of cytokine using the Luminex xMAP technology from Myriad RBM, will be measured to determine the status of the T helper cell polarization.

Memory B cell FluoroSpot

Memory B-cells (MBC) secreting Spike specific-IgG and IgA antibodies will be quantified in PBMCs from selected timepoints using a fluorescent immunospot (FluoroSpot) assay. The spike-specific memory B-cell response will be assessed by plating the in-vitro stimulated (R848 and IL-2) PBMC on an ELISPOT/FluoroSpot plate that is pre-coated with the Spike protein. The activated B-cells will secrete antibodies of different isotypes and specificities, but only those with a specificity to the pre-coated Spike proteins will be captured and detected by fluorescent-conjugated detection antibodies capable of recognizing bound IgG or IgA antibodies. Spike-specific IgG and IgA memory responses will be compared to the total IgG and IgA response seen in wells that are pre-coated with human capture antibodies directed against IgG and IgA and plated with stimulated PBMCs.

8.2.2 Efficacy Assessments

8.2.2.1 Definitions

Virologically-confirmed COVID-19-Like Illness

Defined as a positive result for SARS-CoV-2 by Nucleic Acid Amplification Test (NAAT) on a respiratory sample in association with a COVID-19-like illness.

Serologically-confirmed SARS-CoV-2 Infection

Defined as a positive result in serum for the presence of antibodies specific to the nucleoprotein of SARS-CoV-2 detected by electrochemiluminescence immunoassay (ECLIA).

SARS-CoV-2 Infection

A positive result for SARS-CoV-2 by NAAT on a respiratory sample OR positive result in serum for presence of antibodies specific to the nucleoprotein of SARS-CoV-2 detected by ECLIA.

COVID-19-Like Illness

Symptoms of COVID-19-like illness are as listed below, along with an accompanying tabulation of terms used in the CRFs versus DCs/Memory Aids (Table 8.2).

New onset of any ONE of the following (that persists for a period of at least 24 hours or reoccurs within a 12-hour period):

- Cough (dry or productive)
- Fever (measured temperature > 100.4ºF or > 38ºC)
- Difficulty breathing or shortness of breath
- Anosmia
- Ageusia

[redacted]

- Chilblains (COVID-toes)
- Clinical or radiographic evidence of pneumonia
- Myocarditis, myocardial infarction
- Thromboembolic event (blood clots [eg, pulmonary embolism, deep vein thrombosis, stroke])
- Purpura fulminans

OR

New onset of any TWO of the following that are present at the same time (both symptoms that persist for a period of at least 24 hours or reoccurs within a 12-hour period):

- Pharyngitis
- Chills
- Myalgia
- Fatigue (malaise)
- Headache
- Rhinorrhea or nasal congestion
- Abdominal pain
- At least one of nausea or vomiting
- Diarrhea

Table 8.2: COVID-19-like illness symptoms: CRF and Diary Card/Memory Aid terms

CRF term	Diary Card/Memory Aid term
Cough	Cough
Fever	Temperature measured as > 100.4ºF or > 38ºC
Shortness of breath	Difficulty breathing or feeling short winded
Anosmia	Loss of smell
Ageusia	Loss of taste
Chilblains	Pain, redness, sores in your fingers and toes exposed to cold
Pneumonia	Infection of the lungs
Stroke	Stroke
Myocarditis	Heart inflammation
Myocardial infarction	Heart attack
Thromboembolic event	Blood clots
Purpura fulminans	A type of purplish skin rash

[redacted]

CRF term	Diary Card/Memory Aid term
Pharyngitis	Sore throat
Chills	Chills
Myalgia	Muscle aches and pains
Fatigue (malaise)	Feeling unwell / tired
Headache	Headache
Rhinorrhea	Runny nose
Nasal congestion	Stuffy nose
Abdominal pain	Belly pain
Nausea	Feeling queasy
Vomiting	Throwing up
Diarrhea	Loose stools

8.2.2.2 COVID-19-like Illness Surveillance

Passive Surveillance

Following randomization and vaccination, all participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness listed in the DC at any time during the study or if they seek medical care for their symptoms or if they have a positive COVID-19 test from any other source.

Active Surveillance

Following randomization and vaccination, active surveillance will be used to identify potential COVID-19 clinical illness cases.

All participants will be contacted by study site or delegated call center starting on D57 (2 weeks after D43 contact) and continuing until D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2). The frequency of phone contacts will be once every 2 weeks (± 6 days) or may be completed through alternative contact methods (text message, email, and/or home visit). Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits) as described in the SoA (Section 1.3). After active surveillance has ended at D181 (Cohort 1) or D202 (Sentinel Cohort and Cohort 2), passive surveillance will continue through the end of the study as previously stated above.

Collection of Respiratory Samples

For the duration of the study, the site will arrange for a respiratory sample to be taken if the participant experiences symptoms of COVID-19-like illness (see Section 8.2.2.1). After the onset of symptoms of COVID-19-like illness, the respiratory sample will be obtained as soon as

[redacted]

possible, unless during the first reactogenicity period (D01-D09) when the sample may be collected up to D09, at the Investigator's discretion.

All respiratory samples will be submitted for analysis by SARS-CoV-2 NAAT and a positive result will be considered a virologically-confirmed COVID-19-like illness (see Section 8.2.2.4). The samples (confirmed by SARS-CoV-2 NAAT) will be stored in a SP Sample Biorepository for further viral characterization, if needed.

If the respiratory sample swab cannot be collected, the research site will still collect the information mentioned below.

Reporting of Events Temporally Associated with a COVID-19-like Illness

In addition to obtaining a respiratory sample, the site will collect detailed information about the symptoms, severity and duration of illness, as well as information on healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) and medication use (eg, antibiotics, antivirals). These are also outlined in Table 1.6.

In the event of hospitalization during the course of illness, detailed information on the course of the illness including duration of symptoms, oxygen requirements, laboratory tests, imaging investigations (including computerized tomography), use of mechanical ventilation and other respiratory support medications used, and outcome will be collected.

All participants reporting a COVID-19-like illness will have a 30-day follow-up telephone call.

8.2.2.3 ELECSYS Anti-SARS-CoV-2 ECLIA

Elecsys® (Roche Diagnostics) Anti-SARS-CoV-2 is an immunoassay intended for qualitative detection of antibodies to SARS-CoV-2 in human serum. The assay uses a recombinant protein representing the nucleoprotein antigen. Sample, biotinylated SARS-CoV-2-specific recombinant antigen and SARS-CoV-2−specific recombinant antigen labeled with a ruthenium complex are first incubated and form a sandwich complex. After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M/ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

8.2.2.4 Nucleic Acid Amplification Test (NAAT) for COVID-19 Case Detection

In the assay, respiratory samples will be collected and the RNA will be extracted. The purified template is then evaluated by a NAAT using SARS-CoV-2 specific primers to specifically amplify SARS-CoV-2 targets.

[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 SoA (Section 1.3).

8.3.1 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.

8.3.2 Physical Examinations

At the screening visit, the Investigator or a delegate will perform a targeted physical examination. At Visit 01, a targeted physical examination might be performed based on the participant's medical history and Investigator's discretion. Information will be recorded in the source document.

8.3.3 Vital Signs

Oral pre-vaccination temperature and other vital signs will be systematically collected by the Investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.3.4 Clinical Safety Laboratory Assessments

Urine pregnancy testing will be performed in women of childbearing potential at the screening visit and before each vaccination.

- See Appendix 10.2 for the complete list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
    - If such 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.

[redacted]

- All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual/operating guidelines and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory of choice require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the CRF.

8.4 Adverse Events and Serious Adverse Events

Safety will be described in all study participants.

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).

8.4.1 Sentinel Cohort

SMT Meetings

The participants enrolled in the Sentinel Cohort (see Overall Design, Section 4.1) will be closely followed-up by the SMT (Figure 1.5).

The SMT will perform an unblinded review to evaluate the D01-D03 and D22-D24 safety data and the following safety parameters will be assessed: immediate reactions, solicited injection site and systemic reactions, unsolicited AEs reported as vaccine related by the Investigator, SAEs, and AESIs.

Initial Sentinel Cohort (low-dose; [redacted] µg, N=5)

If any of the below alert threshold criteria are met for the D01-D03 safety data of the low-dose group in the Initial Sentinel Cohort (N=5 participants), a decision will be made as to whether the second injection can be administered:

- ≥ 1 participant experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- ≥ 1 participant experiencing Grade 3 solicited injection site pain
- ≥ 1 participant experiencing Grade 3 unsolicited non-serious reactions (reactions not explained by any other possible etiology)
- Any related SAEs, or, any Intensive Care Unit (ICU) admission for SARS-CoV-2 infection regardless of relationship to vaccination

[redacted]

Initial Sentinel Cohort (ultra-low- [µg) and medium- [µg] dose; N=10 in each group)

If any of the below alert threshold criteria are met for the D01-D03 safety data of the ultra-low- and medium- dose groups in the Initial Sentinel Cohort (N=10 participants in each group), a decision will be made as to whether the second injection can be administered:

- ≥ 2 participants experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- ≥ 2 participants experiencing Grade 3 solicited injection site pain
- ≥ 2 participants experiencing Grade 3 unsolicited non-serious reactions (reactions not explained by any other possible etiology)
- Any related SAEs, or, any ICU admission for SARS-CoV-2 infection regardless of relationship to vaccination

Expanded Sentinel Cohort (all dose-levels)

If any of the below alert threshold criteria are met for the D01-D03 safety data of any dose-level group in the Expanded Sentinel Cohort for the participants enrolled beyond the initial Sentinel Cohort (N= between 15-20 participants, depending on dose-level group [15 potential additional participants added for ultra-low and medium dose levels, and 20 participants added for the low-dose level), a decision will be made as to whether subsequent vaccinations for a specific dose-level or corresponding escalation dose-levels will be allowed to resume or not:

- > 20% of participants experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- > 20% of participants experiencing Grade 3 solicited injection site pain
- > 20% of participants experiencing Grade 3 unsolicited non-serious reactions (reactions not explained by any other possible etiology)
- Any related SAEs, or, any ICU admission for SARS-CoV-2 infection regardless of relationship to vaccination

Ad hoc SMT Meetings

In addition, ad hoc SMTs for any Sentinel Cohort group may occur to evaluate D01-D09 additional safety data, including laboratory data as needed, to better understand safety. Such ad hoc SMT evaluations will inform study progression, especially if any Sentinel Cohort groups reach the time of second vaccination before CS-ESDR-1 takes place. In case of D01-D09 SMT, the parameters listed above for the corresponding Initial or Expanded Sentinel Cohort along with the additional evaluation of laboratory safety parameters will be assessed for:

Initial Sentinel Cohort (low-dose; µg, N=5):

- ≥ 1participant with Grade 3 laboratory AE
- ≥ 1 participant with Grade 2 laboratory AE (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful

Initial Sentinel Cohort (ultra-low- [µg] and medium- [µg] dose; N=10 in each group)

- ≥ 2 participants with Grade 3 laboratory AE
- ≥ 2 participants with Grade 2 laboratory AE (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful

Expanded Sentinel Cohort (all dose-levels)

- > 20% of participants with Grade 3 laboratory AE
- > 20% of participants with Grade 2 laboratory AE (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful.

8.4.2 Early Safety Data Review

Sentinel Cohort Safety Evaluation and Safety Parameters

Two Complete Sentinel ESDRs (CS-ESDR-1 and CS-ESDR-2) will be performed for the Sentinel Cohort. The goal of the CS-ESDRs is to allow the preliminary safety and laboratory parameter assessment of safety data after the first (D01-D09) and the second (D22-D30) vaccine administration to all Initial and all triggered Expanded Cohort participants.

Clinical safety laboratory evaluations will be performed at screening and 8 days after each injection. The first CS-ESDR will be performed for all Sentinel Cohort participants after safety data, including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, is obtained from D01-D09 following the first injection. This unblinded review will be performed by the Sponsor during the SMT meetings.

If no safety signals or major tolerability concerns are identified at CS-ESDR-1, the double-blind enrollment of up to 308 participants (vaccine and placebo groups) for the first vaccination of the Full Enrollment Cohort (Cohort 1 allocated to the single-injection schedule and Cohort 2 allocated to the 2-injection schedule) will be initiated. It is to be noted that the first vaccination in the Full Enrollment Cohort may be delayed until after the second vaccination of some of the Sentinel Cohort groups or even postponed until after CS-ESDR-2, if deemed necessary by the SMT.

It is understood that this review is based on preliminary data that have been validated but not subject to database lock. (The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged.)
The following safety parameters will be assessed as part of the CS-ESDR:

- Immediate reactions
- Solicited injection site and systemic reactions
- Laboratory abnormalities (including hematology, chemistry, coagulation time, and urinalysis)
- Unsolicited AEs reported as vaccine related by the Investigator
- SAEs and AESIs

Enrollment will be paused during the SMT meeting and the sentinel safety parameters noted will be examined. If any of the below criteria are met for the D01-D09 safety and laboratory data, the

data on the particular alert threshold event will be reviewed by the SMT and a decision will be made as to whether subsequent vaccinations in the study will be allowed to resume or not:

- > 20% of participants experiencing Grade 3 systemic reaction (without concurrent infectious disease) that last for at least 3 days at Grade 3 intensity
- > 20% of participants experiencing Grade 3 solicited injection site pain
- > 20% of participants experiencing Grade 3 unsolicited non serious reactions (reactions not explained by any other possible etiology)
- > 20% of participants with Grade 3 laboratory AE
- > 20% of participants with Grade 2 laboratory AE (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful
- Any related SAEs or any ICU admission for SARS-CoV-2 infection regardless of relationship to vaccination

A subsequent safety review (CS-ESDR-2) is planned for the Sentinel Cohort participants during which the unblinded SMT will examine the available D22-D30 safety data post-second vaccination including local and systemic AEs, unsolicited AEs, and biological safety laboratory parameters, and all available MAAEs, SAEs, and AESIs for the Sentinel Cohort participants will also be reviewed. If no safety signals or major tolerability concerns are identified during this period in the Sentinel Cohort, then all participants in Cohort 2 will progress to get the second injection (VAC2). If a safety signal or a major tolerability concern is identified at CS-ESDR-2 for the Sentinel Cohort, then Cohort 2 participants for the corresponding dose-level may not receive their second vaccination.

8.4.3 Halting Rules for Entire Study

An SMT will review the safety data at regular intervals, to identify any new safety signals or safety concerns during the conduct of the study. The SMT is empowered to recommend a pause in both recruitment and/or further vaccination while it investigates any potential signal or concern. Enrollment will be paused during the review and the data will be examined.

Enrollment and/or further vaccination will be paused if the following alert thresholds are identified:

- Any SAEs assessed as related to the vaccine by the Investigator and the Sponsor
- ≥ 2 participants experiencing ulceration, abscess or necrosis at the injection site that is considered related to the study vaccine by the Investigator and the Sponsor
- For each vaccine group advanced to the Full Enrollment Cohort (ie, potentially Groups 1 to 3 and Groups 5 to 7, N=44 participants per group [Table 4.3]), ≥ 4 participants experiencing any Grade 3 AE (systemic reactions lasting for at least 3 days at Grade 3 intensity, unsolicited AEs and/or clinical laboratory abnormality) in the absence of any other etiology
- Events suggestive of vaccine-associated enhanced disease, including:
  - Any death due to SARS-CoV-2 infection

[redacted]

- > 10% of the study population enrolled at any given time is hospitalized due to SARS-CoV-2 infection
- ≥ 3% of study participants ≥ 50 years enrolled at any given time are admitted to the ICU due to SARS-CoV-2 infection
- ≥ 3% of study participants 18 to 49 years enrolled at any given time are admitted to the ICU due to SARS-CoV-2 infection

In addition, ad hoc SMT reviews will occur immediately in the event halting rules are met. Case unblinding may be performed if necessary or if any of the halting rules are met.

8.4.4 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 each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

Solicited injection site reactions will be collected from D01 through D08 after each vaccination.

Solicited systemic reactions will be collected from D01 through D08 after each vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the DCs and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Adverse Events

Unsolicited AEs include unsolicited non-serious AEs and SAEs. The intensity grading scale for unsolicited non-serious AEs is presented in Appendix 10.3.5.1.2. Unsolicited non-serious AEs will be collected from D01 to D22 after each vaccination.

SAEs will be collected and assessed throughout the study, ie, before the start of study intervention but after obtaining informed consent until 12 months after the last vaccination (up to D366 for Cohort 1 and up to D387 for Sentinel Cohort and Cohort 2) or the day of study discontinuation for participants who discontinue permanently. However, before the first study intervention administration, only SAEs related to study procedures are to be collected (eg, SAEs related to blood sampling or study procedure performed during a screening visit).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the CRF.

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 AE or SAE 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.

[redacted]

Medically Attended Adverse Events

MAAEs will be collected at any time during the study.

Adverse Events of Special Interest

AESIs will be collected at any time during the study.

See Section 8.4.9 for the list of AESIs.

8.4.5 Method of Detecting AEs and SAEs

Individual DCs, 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 DCs 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 an authorized designee will interview the participants to collect the information recorded in the DC 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 authorized designee using a web-based CRF. Any information that was not documented in the DC will first be captured in the source document and then reported electronically.

The 12-month (post-last injection) follow-up will be done by interviewing participants during a visit (or over the telephone for participants who discontinue early from the study) using a questionnaire to capture SAEs and AESIs, if applicable.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.6 Follow-up of AEs and SAEs

Unless a participant refuses further contact, each participant who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the participant's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

[redacted]

8.4.7 Regulatory Reporting Requirements for SAEs

- 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 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.
- For all studies except those investigating medical devices, 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.
- An Investigator who receives an Investigator safety report describing an 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.

8.4.8 Pregnancy

Pregnancy is an exclusion criterion for enrollment in this study, but a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected by the Investigator after the start of study intervention and until delivery and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.
- The collection period of pregnancy information will correspond at least to the period during which the participant is requested to be under contraception. (according to protocol: effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination). If there are any pregnancies during this period, follow-up should be conducted up to delivery: this will be covered by the 12-month surveillance of the study.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.9 Adverse Events of Special Interest

AESIs will include:

- Protocol-specified AESIs: Anaphylactic reactions, generalized convulsion, Guillain-Barré Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), thrombocytopenia, and vasculitides
- New-onset chronic medical conditions (NOCMCs)

[redacted]

- AESIs related to SARS-CoV-2 infection and COVID-19 disease (see Appendix 10.5).

8.4.10 Medically Attended Adverse Events

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

8.5 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 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

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7 Pharmacodynamics

As with most vaccines for active immunization, the mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. Therefore, the pharmacodynamic profile of the investigational study intervention is defined by its immunogenicity profile.

8.8 Genetics

Genomic analysis for immune cell profiling and sequencing as related to the exploratory endpoints in establishing biomarkers or vaccine-induced molecular signatures to characterize the immune profiles associated with SARS-CoV-2 vaccination may be performed.

8.9 Biomarkers

Besides the biomarkers described in the immunogenicity and efficacy assessments sections (Section 8.2.1.1 and Section 8.2.2, respectively), other emerging biomarkers may be evaluated in this study which may be relevant for evaluating scientific aspects of COVID-19 illness, or SARS-CoV-2 infection, or for the evaluation of effect modification, correlates of risk/protection, or participants' baseline characteristics.

[redacted]

8.10 Immunogenicity Assessments

See Section 8.2.1.1.

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization will be collected as part of COVID illness in this study (see Section 8.1 and Section 8.2.2.2), as well as for SAE narrative and categorization.

9 Statistical Considerations

9.1 Statistical Hypotheses

All analyses will be descriptive; no hypotheses are planned to be tested.

9.2 Sample Size Determination

This is a first-in-human study to assess the safety profile and immune responses to different doses of the study vaccine when compared to placebo. The study targets enrollment of approximately 333 participants 18 years of age and older, including the 5 participants already vaccinated in the low-dose group. The actual number of participants enrolled will depend on which dose-level groups are allowed to be evaluated in the Sentinel Cohort and the Full Enrollment Cohort. The number may be higher if Expanded Sentinel Cohorts are exercised for all dose-levels, and if all dose-levels progress to the Full Enrollment Cohort (maximum number of study participants approximately 383); conversely, the number may be lower if not all the dose-levels are evaluated in the Sentinel Cohort or/and not all the dose-levels progress to the Full Enrollment Cohort.

No formal power calculation has been performed. The sample size was determined based on logistical considerations and common practices for first-in-human trials.

Vaccine arms will be aggregated to perform complementary assessments on the following main effects: age (18-49 years, ≥ 50 years), dose (ultra-low, low, medium), and injection schedule (1-injection, 2-injection).

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants with a dose-level group that has been allocated by IRT
Safety Analysis Set (SafAS)	Subset of enrolled participants who have received at least 1 injection of study intervention. Participants will have their safety analyzed according to the study intervention they actually received.

[redacted]

Population	Description
	Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full Analysis Set (FAS)	Subset of enrolled participants who received at least 1 injection of the study intervention. Participants will be analyzed according to the intervention to which they were enrolled.
Per-Protocol Analysis Set (PPAS)	Subset of the FAS. Participants presenting with at least 1 of the following relevant conditions will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not complete the protocol-defined vaccination schedule • Participant received a study intervention other than the one that he/she was randomized to receive • Preparation and/or administration of study intervention was not done as per-protocol • Participant did not receive study intervention in the proper time window • Participant received an authorized/approved COVID-19 vaccine prior to D36 visit • Participant with a positive test result in the ELISA and/or neutralization test at baseline Additional conditions for exclusion may be identified during the review of protocol deviations; such conditions will be documented in the Statistical Analysis Plan (SAP).
Per-Protocol Analysis Set for Immunogenicity (PPAS-IAS)	Subset of PPAS excluding participants who provided all post-dose serology samples outside the proper time window or no post-dose serology sample was drawn.
Per-Protocol Analysis Set for AIT (PPAS-AIT)	Subset of PPAS excluding participants who provided all post-dose AIT samples outside the proper time window or no post-dose AIT sample was drawn.

9.4 Statistical Analyses

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.

[redacted]

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or newer (SAS Institute, Cary, North Carolina, USA).

9.4.1 General Considerations

All analyses will be descriptive. Summaries will be provided for main effects (see Section 9.2) as well as individual study arms. Details will be provided in the SAP.

9.4.2 Primary Endpoints

9.4.2.1 Immunogenicity

The primary endpoints for the evaluation of immunogenicity are based on neutralizing antibody titers, which will be measured with the neutralization assay. The statistical analyses that will be performed for the following primary endpoints are as presented in Table 3.1.

Pre-vaccination titers at < LLOQ will be converted to half LLOQ.

The 95% confidence intervals (CIs) for the geometric mean titers (GMTs)/geometric mean concentrations (GMCs) and GMT ratios will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of GMTs will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the 2 sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Additionally, to evaluate independent determinants of primary immunogenicity endpoints, regression models may be constructed for log-transformed titers and occurrence of neutralizing antibody seroconversion. For continuous type of dependent variable, linear models will be utilized; for binary type of dependent variable, logistic regression model will be utilized. Explanatory/independent variables inserted in these models would include main (aggregate) effects including age effects and injection schedule effect.

Immunogenicity analyses will be performed on PPAS-IAS, unless otherwise specified.

9.4.2.2 Safety

The primary endpoints for the evaluation of safety are as presented in Table 3.1. Primary safety endpoints will be summarized by vaccine group, as well as aggregate groups specified in the SAP. The 95% CIs will be calculated using the Clopper-Pearson method.

The SafAS will be used for the safety analyses.

9.4.3 Secondary Endpoints

9.4.3.1 Immunogenicity

The secondary endpoints for the evaluation of immunogenicity are as presented in Table 3.1.

[redacted]

The 95% CIs for the antibody titer (or concentration) and ratio will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of antibody titer (or concentration) will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Regression models may be utilized for further assessment of secondary immunogenicity endpoints, as described in Section 9.4.2.1.

Immunogenicity analyses will be performed on PPAS-IAS, unless otherwise specified.

9.4.3.2 Efficacy

Virologically-confirmed COVID-19-like illness is defined by the occurrence of a COVID-19 illness as described in Section 8.2.2.1, associated with a positive NAAT for SARS-CoV-2 in a respiratory sample.

Serologically-confirmed SARS-CoV-2 infection is defined as a change from negative to positive (see Section 8.2.2.1) in the non-S immunoassay from any post-baseline sampling time-point compared to the baseline value, as measured in a SARS-CoV-2 Nucleoprotein specific antibody detection immunoassay.

Correlates of risk/protection analysis will be performed based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization or binding antibody (ELISA), considering cases of virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection as defined above. Detailed statistical methods will be described in the SAP.

Efficacy analyses will be performed on FAS and PPAS-IAS, unless otherwise specified.

9.4.4 Exploratory Endpoints

9.4.4.1 Immunogenicity

The AIT subset analyses will be defined in the SAP. The AIT subset analyses will be based on PPAS-AIT set. For this subset, Th1 and Th2 cytokines will be measured and summarized for individual and aggregate study arms.

The ratio between binding antibody (ELISA) concentration and neutralizing antibody titer will be summarized for individual and aggregate study arms. The ratio (neutralizing antibody/binding antibody) will be calculated as difference in $\log_{10}$ scale and with the 95% CIs calculated using normal approximation will be provided. The analyses will be performed on PPAS-IAS, unless otherwise specified.

[redacted]

9.5 Interim Analyses

A preliminary interim analysis will be performed on safety and immunogenicity data collected up to D43 for participants enrolled into the Sentinel Safety Cohorts. Database will be cleaned with a partial database lock conducted.

A key interim analysis will be performed on data collected for primary immunogenicity and exploratory AIT subset objectives obtained up to D36 and primary safety objectives through D43 inclusive of both Sentinel and Full Enrollment Cohorts, upon the data availability and when a partial database lock has been conducted. Statistical analysis of data described above will be conducted to support further investigating the study vaccine formulation. The analysis results of the interim analysis (inclusive of the Full Enrollment Cohort) will also be generated to communicate with regulatory agencies. The study blind will be broken at the group level to the Sponsor at that time.

Harm analysis assessed based on split of COVID-19 cases will be conducted based on SafAS at all planned interim analyses. Participants will be analyzed according to the group to which they were randomized. For the assessment, all vaccine arms will be pooled, and all placebo arms will be pooled as well. The timing of the first harm assessment is planned at the interim analysis and will be based on data up to D43.

The assessment for COVID-19 will be implemented separately using a one-sided conditional exact binomial test of H0: $p \leq$ "number of participants in the pooled vaccine arm"/"total number of participants" versus H1: $p >$ "number of participants in the pooled vaccine arm"/"total number of participants", where p is the binomial probability that a case participant is assigned to the vaccine group conditional on the observed total number of cases. The test will be performed at the same pre-specified one-sided nominal/unadjusted alpha-level of 0.05 (unadjusted). The bounds for harm monitoring are computed under the null hypothesis that VE=0%.

If a null hypothesis is rejected and boundary is met, SMT will be notified immediately of the potential harm signal to make an assessment of whether modifications in study conduct and/or monitoring should be implemented.

Another interim analysis will be performed on data collected for immunogenicity, safety, efficacy, and harm up to the 3-month time point (D91 for Cohort 1 and D112 for Sentinel Cohort and Cohort 2).

After the 6-month data (D181 for Cohort 1 and D202 for Sentinel Cohort and Cohort 2) have been collected, a further interim analysis will be performed on immunogenicity, safety, and efficacy endpoints.

A final analysis for all data collected will be conducted once the 12-month safety data have been collected and the final database lock has occurred.

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 (see also Section 8.4.1 for Sentinel Cohort dose-escalation, Section 8.4.2 for CS-ESDR details, and Section 8.4.3 for halting rules for the entire study).

The SAP will describe the planned interim analyses and CS-ESDRs in greater detail.

[redacted]

9.6 Data Monitoring Committee (DMC)

Not applicable.

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.

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
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, protocol amendments, 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
- 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 (in addition to summaries required from the Sponsor)
  - 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

[redacted]

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 he/she 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 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- 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 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 IRB/IEC 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 IRB/IEC 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 re-consented to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized 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 Sanofi Pasteur prior to submission to the IRB/IEC for approval.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR. 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 (36).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the ICF.
- The participant must be informed that his/her 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.
- 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.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum, respiratory, or peripheral blood mononuclear cell (PBMC) samples will be securely stored at a Sanofi Pasteur facility or Contract Research Organization up to 25 years after the end of the study. Unused samples may also be sent to another long-term repository, as necessary. These samples 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.

[redacted]

The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they 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.

In addition, participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for tests not related to the study objectives. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

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.

10.1.6 Dissemination of Clinical Study Data

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.

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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

[redacted]

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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).
- Study monitors will perform ongoing source data verification 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.
- 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.

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, DCs, 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.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered the date of the first visit planned in the SoA (Section 1.3) of the first participant.

[redacted]

The Sponsor 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:

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, 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 10.1 will be performed by the site-selected local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- A urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) will be performed at screening and before each vaccination. Refer to Section 5.1.1 and Section 5.1.2 for pregnancy inclusion criteria.

[redacted]

Table 10.1: Protocol-required safety laboratory assessments

Laboratory assessments	Time period for assessment	Parameters

Hematology	Cohort 1: Screening (between -D04 and -D01) and V02 (D09)
	Sentinel Cohort & Cohort 2: Screening (between -D04 and -D01), V02 (D09), and V04 (D30)
		• White blood cell (WBC) count with differential:
		  ○ Neutrophils
		  ○ Lymphocytes
		  ○ Monocytes
		  ○ Eosinophils
		  ○ Basophils
		• Hemoglobin
		• Platelet count

Clinical Chemistry	Cohort 1: Screening (between -D04 and -D01) and V02 (D09) Sentinel Cohort & Cohort 2: Screening (between -D04 and -D01), V02 (D09), and V04 (D30)	• Sodium • Potassium • Blood Urea Nitrogen • Creatinine • Glucose (nonfasting) • Aspartate aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT) • Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT) • Alkaline phosphatase • Total bilirubin • Direct bilirubin • Total protein
Coagulation parameters	Cohort 1: Screening (between -D04 and -D01) and V02 (D09) Sentinel Cohort & Cohort 2: Screening (between -D04 and -D01), V02 (D09), and V04 (D30)	• PT • PTT • INR
Routine Urinalysis	Cohort 1: Screening (between -D04 and -D01) and V02 (D09) Sentinel Cohort & Cohort 2: Screening (between -D04 and -D01), V02 (D09), and V04 (D30)	• Glucose, protein, blood, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)

[redacted]

Laboratory assessments	Time period for assessment	Parameters
Other Screening Tests	Cohort 1: Screening (between -D04 and -D01), V01 (D01) Sentinel Cohort & Cohort 2: Screening (between -D04 and -D01), V01 (D01), V03 (D22)	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)*
	Screening (between -D08 and -D01). Results for serology tests obtained within 4 weeks prior to V01 will be accepted.	• HIV antibody • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody
	Screening (between -D04 and -D01; All participants)	SARS-CoV-2 antibody

*To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile

It is to be noted that COVID-19 antibody test and blood and urine sampling for safety tests may be performed on the day of enrollment as long as the results to assess exclusion criteria are available prior to enrollment.

Investigators must document their review of each laboratory safety report.

For all participants, laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

[redacted]

10.3 Appendix: Adverse Events: 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 patient or 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, electrocardiogram [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 drug-drug 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. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless 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.

[redacted]

- 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:

All noxious and unintended responses to a study intervention related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a study intervention" means that a causal relationship between a study intervention and an AE is at least a reasonable possibility)

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the study intervention administered) that occur within the first 30 minutes after vaccination.

Medically Attended Adverse Event:

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 email 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.

Injection Site Reaction/Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site. Injection/administration site reactions are commonly inflammatory reactions. They are considered to be related to the study intervention administered.

Systemic Adverse Event/Adverse Reaction:

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

Systemic AEs assessed as related to study intervention are referred as systemic ARs. Solicited systemic reactions occurring during the specified collection period are always considered related to the study vaccine even if there is evidence or alternative etiology.

[redacted]

Adverse Event 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. 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.

New-Onset Chronic Medical Conditions (NOCMCs):

NOCMCs are defined as any new ICD-10 diagnosis (10th revision of the International Statistical Classification of Diseases and Related Health Problems) that is applied to the participant during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

Reactogenicity/Solicited Reactions:

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 and the next 7 days).

By definition, solicited reactions are considered as being related to the study intervention administered.

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

Unsolicited Adverse Event/Adverse Reaction:

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/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (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 study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death

[redacted]

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 detained (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. When 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 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. Other important medical event

- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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 are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, new-onset diabetes or autoimmune disease.

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.

[redacted]

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 in the CRF.
- 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 injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the study intervention 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. 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 will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered[a] 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 an 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 first vaccination (screening phase, if applicable)

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

[redacted]

- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there is 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.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- 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 make an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causal relationship in light of follow-up information and send a 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 completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Adverse events likely to be related to the study intervention, whether serious or not, 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.

[redacted]

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) in order 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).
- Details regarding SAE reporting can be found in the Operating Guidelines.

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: 570-957-2782
  - In PDF format to the following email address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.coam
  - By express mail, to the following address:

    Global PharmacoVigilance, Sanofi Pasteur
    Discovery Drive
    Swiftwater, PA 18370

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 6.3.2.

[redacted]

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 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

[redacted]

Table 10.2: Solicited injection site reactions: terminology, definitions, and intensity scales

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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

MedDRA: Medical Dictionary for Regulatory Activities
* For the subjective reaction of pain, participants will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 10.3: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Chills
Diary card term	Temperature	Headache	Feeling unwell or feeling tired	Muscle aches and pains	Joint pain	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	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.	Pain in a joint or joints	Sensation of cold

[redacted]

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Arthralgia**	**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**	**Arthralgia**	**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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions but fever, participants will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, 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. The optimal time for measurement is the evening, when body temperature is the highest. 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.

10.3.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

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

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

10.3.5.2 Tables for Laboratory Abnormalities

The pre-defined intensity thresholds for laboratories abnormalities are shown in Table 10.4.

[redacted]

Table 10.4: Intensity thresholds for laboratory abnormalities

Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Above normal WBC – cell/mm^3	10,800 – 15,000	15,001 – 20,000	≥ 20,001
Below normal WBC – cell/mm^3	2,500 – 3,500	1,500 – 2,499	≤ 1,499
Hemoglobin (Female) – gm/dL	11.0 – 12.0	9.5 – 10.9	≤ 9.4
Hemoglobin (Female) (Change from baseline value) – gm/dL	Any decrease – 1.5	1.6 – 2.0	≥ 2.1
Hemoglobin (Male) – gm/dL	12.5 – 13.5	10.5 – 12.4	< 10.5
Hemoglobin (Male) (change from baseline value) – gm/dL	Any decrease – 1.5	1.6 – 2.0	≥ 2.1
Platelets decreased – cell/mm^3	125,000 – 140,000	100,000 – 124,000	≤ 99,000
Absolute neutrophil decrease – cell/mm^3	1,500 – 2,000	1,000 – 1,499	< 999
Absolute lymphocyte decrease – cell/mm^3	750 – 1,000	500 – 749	< 499
Absolute eosinophil – cell/mm^3	650 – 1500	1501 - 5000	> 5000
Sodium – Hyponatremia – mEq/L	132 – 134	130 – 131	< 130
Sodium – Hypernatremia – mEq/L	144 – 145	146 – 147	> 148
Potassium – Hyperkalemia – mEq/L	5.1 – 5.2	5.3 – 5.4	> 5.4
Potassium – Hypokalemia – mEq/L	3.5 – 3.6	3.3 – 3.4	< 3.3
Blood Urea Nitrogen (BUN) – mg/dL	23 – 26	27 – 31	> 31 or require dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	≥ 2.1 or requires dialysis
Glucose – Hyperglycemia (random) – mg/dL	110 - 125	126 - 200	> 200
Total protein – Hypoproteinemia – g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0
LFT (ALT, AST) (Increase by factor)	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	≥ 5.1 ULN
Alkaline phosphate (Increase by factor)	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	≥ 3.1 ULN
Bilirubin – with any increase in LFT (Increase by factor)	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	≥ 1.51 ULN
Bilirubin – with normal LFT (Increase by factor)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	≥ 2.1 ULN

[redacted]

Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
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
Urine - glucose	Trace	1+	2+
Urine - protein	Trace	1+	2+
Urine – blood (microscopic - RBCs per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; dL, deciliter; gm, gram; L, liter; LFT, liver function test; mEq, milliequivalent; mg, milligram; mm^3, cubic millimeter; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; ULN, upper limit of normal; WBC, white blood cell.

[redacted]

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal 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) Post-menopausal female
   - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (37) level in the post-menopausal range may be used to confirm a post-menopausal 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 post-menopausal status before study enrollment.

COLLECTION OF PREGNANCY INFORMATION

The collection period of pregnancy information will correspond at least to the period during which the participant is requested to be under contraception. (according to protocol: effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination). If there are any pregnancy during this period, follow-up should be conducted up to delivery: this will be covered by the 12-month surveillance of the study.

[redacted]

Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy.
- 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 to 8 weeks 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.
- 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.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- 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 8.4.7. 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.
- In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the participant will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).
- If primary series have been completed and the delivery occurs between the primary series and the booster, the booster dose can be administered. However, if vaccination is a contraindication for lactation (ie, live-attenuated vaccine), the participant may not be vaccinated with a booster dose.

[redacted]

10.5 Appendix: AESIs

Protocol-Specified AESIs

- Anaphylactic reactions
- Generalized convulsion
- Guillain-Barré Syndrome (GBS)
- Acute disseminated encephalomyelitis (ADEM)
- Thrombocytopenia
- Vasculitides
- NOCMCs

AESIs Related to SARS-CoV-2 Infection and COVID-19 Disease

Immunologic

- Enhanced disease following immunization

Respiratory

- Acute respiratory distress syndrome

Cardiac

Acute cardiac injury including:

- Microangiopathy
- Heart failure and cardiogenic shock
- Stress cardiomyopathy
- Coronary artery disease
- Arrhythmia
- Myocarditis, Pericarditis

Endocrine

- Pancreatitis
- Subacute thyroiditis

Hematologic

Coagulation disorder

- Deep vein thrombosis
- Pulmonary embolus
- Cerebrovascular stroke
- Limb ischemia
- Hemorrhagic disease

Musculoskeletal

- Rhabdomyolysis

[redacted]

Renal

- Acute kidney injury

Gastrointestinal

- Liver injury

Neurologic

- GBS
- Anosmia, Ageusia
- Meningoencephalitis

Dermatologic

- Chilblain-like lesions
- Single organ cutaneous vasculitis
- Erythema multiforme

10.6 Appendix: Risk-based Approach

ICH E6-R2 guideline 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.

[redacted]

10.7 Appendix: Abbreviations

2P	double proline
Ab	antibody
ADEM	acute disseminated encephalomyelitis
AE	adverse events
AESI	adverse event of special interest
AIT	Additional Immunological Tests
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	adverse reactions
BL	blood sample (#)
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMI	cell-mediated immunity
CRF	case report form
CS-ESDR	Complete Sentinel Early Safety Data Review
D	Day
DC	diary card
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme-linked immunosorbent assay
ESDR	Early Safety Data Review
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GBS	Guillain-Barré Syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice

[redacted]

GDPR	General Data Protection Regulation
GMC	geometric mean concentration
GMT	geometric mean titer
GPV	Global Pharmacovigilance
HA	hemagglutinin
hCG	human chorionic gonadotropin
HCoV	Human Coronavirus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committees
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Boards
IRT	Interactive Response Technology
[redacted]	[redacted]
[redacted]	[redacted]
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
NAAT	nucleic acid amplification test
NHP	non-human primate
NOAEL	no-observed-adverse-effect level

[redacted]

NOCMC	new-onset chronic medical conditions
OD	optical density
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
PPAS	per-protocol analysis set
PPAS-AIT	per-protocol analysis set for AIT
PPAS-IAS	per-protocol analysis set for immunogenicity
PT	prothrombin time
PTT	partial thromboplastin time
RMO	Responsible Medical Officer
RNA	ribonucleic acid
S	spike
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMT	Safety Management Team
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TC	telephone call
Th	T-helper cell
VAC	Vaccination (as in Vaccination #)
US	United States
[redacted]	[redacted]
WOCBP	Woman of Childbearing Potential

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12 Sponsor Signature Page

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Document Number CLI_00321998	**Version Number** 3.0
Project Code COVID-19 mRNA	
Artifact Name Protocol Body	

	Approver Name	**Date** (Universal Time)	**Reason for Signature**
Approval	[redacted]		

[redacted]