NCT04798027

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

A first-in-human Phase I/II, multi-center study comprised of 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), Honduras, Brazil and Australia

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VAW00001
Development Phase:	Phase I/II
Sponsor:	Sanofi Pasteur Inc.
Investigational Product(s):	SARS-CoV-2 mRNA vaccine
Form / Route:	Suspension / IM injection
Indication For This Study:	Active immunization for the prevention of SARS-COV-2 disease
Version and Date of the SAP core body part:	Version 5.0, 2Sep2022

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List of Abbreviations

ADEM	acute disseminated encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
AIT	additional immunological tests
AR	adverse reaction
ASC	antibody secreting cell
BL	blood sample
CI	confidence interval
CRF	case report form
CSR	clinical study report
CS-ESDR	Complete Sentinel Early Safety Data Review
COVID-19	coronavirus disease 2019
D	day
eCRF	electronic case report form
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme linked immunosorbent assay
FAS	full analysis set
GBS	Guillain-Barré Syndrome
GM	geometric mean
GM-CSF	granulocyte-macrophage-colony-stimulating factor
GMC	geometric mean concentration
GMT	geometric mean titer
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
IFN	interferon
IL	interleukin
IRT	interactive response system
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger ribonucleic acid
NA	not applicable

NAAT	nucleic acid amplification test
NOCMC	new-onset chronic medical condition
PBMC	peripheral blood mononuclear cell
PCA	principal component analysis
PPAS	per-protocol analysis set
PPAS-IAS	per-protocol analysis set for immunogenicity
PPAS-AIT	per-protocol analysis set for AIT subset
PT	preferred term
PV	Pharmacovigilance
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
RMO	Responsible Medical Officer
RNA	ribonucleic acid
S	spike
SAE	serious adverse event
SafAS	safety analysis set
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SMT	Safety Management Team
SOC	system organ class (primary)
Th	T helper cell
THGM	granulocyte-macrophage-colony-stimulating factor-producing T helper
TLF	table(s), listing(s), and figure(s)
TNF	tumor necrosis factor
ULOQ	upper limit of quantification
US	United States
V	visit
VAC	vaccination
VE	vaccine efficacy

1 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 coronavirus disease 2019 (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) (1). 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 (2).

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 entire sequence for the prefusion stabilized form of the SARS-CoV-2 S protein with 2 sets of mutations, first in the S2 portion of the S protein that locks the expressed S protein in the prefusion conformation, and second 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 had 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]) supported 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 was manufactured by Translate Bio.

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), Honduras, Brazil, and Australia. 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] and the Sponsor introduced 4 changes through a protocol amendment:

1) Add an “ultra-low-dose” arm of [redacted] µg [redacted] to evaluate [redacted]

[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 had yet to start enrollment (ie, ultra-low- and medium-dose-levels).
3) Include an option to 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 was also extended to the ultra-low- and medium-dose groups, if needed.
4) Decrease the number of placebo recipients in the Full Enrollment Cohort.

After the planned preliminary interim of the Sentinel Cohort participants, a decision to discontinue the development of the mRNA COVID-19 vaccine was made. On September 27, 2021, all Investigators were informed to terminate further vaccinations and enrollment. All enrolled participants were to be unblinded to allow them to make their decision to receive an authorized COVID-19 vaccine. All clinical sites were to contact participants to inform them of the discontinuation of further study vaccinations, told what intervention they received and invited to come in for an unscheduled visit for counseling to answer any questions about the study, to discuss available options for receipt of an approved /authorized COVID vaccination, and were requested to provide unscheduled blood draw for serological assessment (UBXX). Participants were informed that additional D22 or D36 blood draws for serological assessment would be appreciated but are not mandatory. No protocol defined schedule visits or blood draws at timepoints later than D36 were required. Monitoring for SAEs, AESIs, medically attended AEs, and pregnancy and collection of influenza and COVID-19 vaccines were continued with safety calls. On March 15, 2022, after concurrence from regulatory authorities, Investigators were notified of the decision to end the study at the 6-month safety follow-up instead of 12-month follow-up.

This version 5.0 of SAP is updated for the final unblinded analysis. The sections of Trial Objectives and Trial Design and Plan are kept the same with the final protocol, but modifications are made in Section 4 and Section 5 for endpoint derivation, statistical methods, and populations used in analyses, to reflect the changes needed for the final analyses.

2 Trial Objectives

2.1 Primary Objectives

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.

Immunogenicity

To describe the neutralizing antibody profile at D01, D22, and D36 of each study intervention group.

2.2 Secondary Objectives

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.

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.

2.3 Exploratory Objectives

Immunogenicity

1) To assess the T-cell cytokine profile at D01, D22 and D36 in the Additional Immunological Tests (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.

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.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase I/II, first-in-human, multi-center, safety and immunogenicity study comprised of 2 sequential cohorts: a lead-in, open-label, dose escalation Sentinel Cohort (initial target of 25 participants) with Complete Sentinel Early Safety Data Reviews (CS-ESDRs), followed by a

randomized, modified double-blind, dose-ranging, 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), 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 US and Honduras.

Participants in the Initial Sentinel Cohort were 18-49 years of age at enrollment and were assigned to receive 2 injections of one of the 3 dose-levels (ultra-low-dose [[redacted] µg], low-dose [[redacted] µg] and medium-dose [[redacted] µg]) of the study vaccine, 21 days apart, in a stepwise open-label manner. In case an alert threshold was met in a dose-level group in the Initial Sentinel Cohort, the corresponding dose-level group could be expanded to reach a total of approximately 25 participants as shown in Figure 1.5 of the protocol. Details of the planned safety parameters and alert thresholds to be examined for the Sentinel Cohort safety analysis are provided in Section 8.4.1 and Section 8.4.2 of the protocol. 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) were to receive a single injection of study intervention while participants in Cohort 2 of the Full Enrollment Cohort (hereafter referred to as Cohort 2) were to 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). Halting rules for the Entire Study are provided in Section 8.4.3 of the protocol.

The study targeted enrollment of approximately 333 participants 18 years of age and older, [redacted]. The actual number of participants enrolled depended on which dose-level groups were allowed to be evaluated in the Sentinel Cohort and the Full Enrollment Cohort. The number could have been higher if Expanded Sentinel Cohorts were 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 could have been lower if not all the dose-levels were evaluated in the Sentinel Cohort or/and not all the dose-levels progress to the Full Enrollment Cohort. A subset of up to 77 randomly selected participants in Cohort 2 was to be included in an AIT subset. Please refer to Table 4.2 and Table 4.3 of the protocol for the planned sample size in Sentinel Cohort and Full Enrollment Cohort.

Further details about the planned study procedures are given in Table 1.3 to Table 1.6 of the protocol.

It should be noted that throughout the study, the Sponsor's Safety Management Team (SMT) core members, consisting of Clinical Team Leader (Responsible Medical Officer [RMO]), Study Biostatistician, Pharmacovigilance Science Expert, and Global Safety Officer, continuously reviewed blinded safety data, except for the safety reviews for the Sentinel Cohort, during which unblinded safety data was reviewed. The blind was broken at the group level for the Sponsor at the time of each interim analysis. Further unblinding could have been performed if any of the halting rules were met (see Section 8.4.3 of the protocol) or if there was any safety concern.

Participants were followed over the duration of the study for development of symptoms of COVID-19-like illness. Participants received surveillance phone calls every 2 weeks (± 6 days starting after the D43 contact to approximately 6 months) or could have been 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 experienced symptoms of COVID-19-like illness. In addition, all participants had been instructed to contact the site if they experienced 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 of protocol.

Participants were free to receive an authorized/approved COVID-19 vaccine. If the participant received an authorized/approved COVID-19 vaccine, this information was collected and the participant's data up to the point of receipt of an authorized/approved COVID-19 vaccine was included in the analysis. Participants continued to be followed for the duration of the study as per scheduled visits and procedures. Participants were invited to a visit prior to receiving the vaccine and requested to provide a blood sample for immunological assessment. Participants were not to receive the second vaccination if they had received an authorized/approved COVID-19 vaccine between the first and second scheduled vaccination.

3.2 Trial Plan

The graphical design of VAW00001 study is as presented in Figure 1.1 to Figure 1.5 in the protocol.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For Assessment methods, see protocol Section 8.2.1.1 for primary immunogenicity; see protocol Section 8.3.4 and Section 8.4 for primary safety.

4.2 Secondary Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For Assessment methods, see protocol Section 8.2.1.1 and Section 8.2.1.2 for secondary immunogenicity; see protocol Section 8.2.2 for secondary efficacy.

4.3 Exploratory Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For exploratory immunogenicity assessment methods, see protocol Section 8.2.1.2.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

The main safety analysis will include all events or reactions with time of onset before the date of receiving a non-study authorized/approved COVID-19 vaccine and including only the corresponding safety data collected before the date of receiving a non-study authorized/approved COVID-19 vaccine. The endpoints derivations for safety analysis are detailed in the following sections. Conducting main analysis with data censored by the date of receiving a non-study authorized/approved COVID-19 vaccine will only be applied to some selected endpoints. Details on the conduct of the main safety analysis for those endpoints are provided in the following subsections. Other endpoints will be analyzed as usual. Events or reactions with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

For measurable injection site reactions:

- None: > 0 to < 25 mm
- Grade 1: ≥ 25 to ≤ 50 mm
- Grade 2: ≥ 51 to ≤ 100 mm
- Grade 3: > 100 mm

For Fever:

- None: < 38.0°C or < 100.4°F
- Grade 1: ≥ 38.0°C to ≤ 38.4°C or ≥ 100.4°F to ≤ 101.1°F
- Grade 2: ≥ 38.5°C to ≤ 38.9°C or ≥ 101.2°F to ≤ 102.0°F
- Grade 3: ≥ 39.0°C or ≥ 102.1°F

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

1) Solicited reactions (except fever/pyrexia) with an Investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as “None”.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3. Note: the intensity could be considered “None” (not a reaction) in the analysis

despite being considered a reaction by the Investigator (eg, swelling measurement > 0 mm but < 25 mm in adults).

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

4.4.1.1.2 Maximum Overall Intensity

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

Note: The maximum intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the Investigator (eg, swelling measurement > 0 mm but < 25 mm in adults). The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

For those participants receiving a non-study authorized/approved COVID-19 vaccine (eg, on Day X) within the solicited collection period, the maximum intensity of solicited reactions in main safety analysis is derived on daily intensities from D01 to Day X.

4.4.1.1.3 Presence

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

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (ie, reaction occurs over 2 separate periods of time intervened by at least 1 daily intensity, Missing or None) then the time of onset is the first day of the first occurrence. The categories for time of onset are presented in Table 4.1.

Table 4.1: Categories for time of onset

Injection Site and Systemic Reactions (D01-D08)
D01-D04
D05-D08

Main safety analysis will include only those solicited reactions with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine. Events or reactions with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. But if a reaction is ongoing at the time of receiving an authorized/approved COVID-19 vaccine, the daily intensities on or after that point will not be considered. Number of days of occurrence on the solicited period with a specified intensity may also be derived. The categories for number of days of occurrence during the solicited period are presented in Table 4.2.

The number of days of occurrence for main safety analysis will treat the date of receiving non-study authorized/approved COVID-19 vaccine as the censored date and only daily intensities that occurred before the vaccination date will be analyzed.

Table 4.2: Categories for number of days of occurrence during the solicited period

Injection Site Reactions (D01-D08)	Systemic Reactions (D01-D08)
1-3 days	1-3 days
4-7 days	4-7 days
8 days	8 days

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period.

The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing. If a participant received a non-study authorized/approved COVID-19 vaccine within the solicited period and the solicited reaction is ongoing at the time of the receipt of the authorized/approved COVID-19 vaccine, the overall number of days of occurrence will be analyzed as Missing for main safety analysis.

The categories for overall number of days of occurrence are presented in Table 4.3.

Table 4.3: Categories for overall number of days of occurrence

Injection Site Reactions (D01-D08)	Systemic Reactions (D01-D08)
1-3 days	1-3 days
4-7 days	4-7 days
8 days or more	8 days or more
Missing	Missing

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity in the ongoing period. The Investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

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

If a participant received a non-study authorized/approved COVID-19 vaccine within the solicited period, the ongoing status will be derived as "Missing".

4.4.1.2 Unsolicited Adverse Events

Unsolicited AEs include non-serious unsolicited adverse events (AEs), immediate unsolicited AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), and medically-attended adverse events (MAAEs). Analysis for unsolicited AEs only include those AEs collected within 21 days after each injection. SAEs, AESIs, and MAAEs collected out of this range will only be presented in the analysis of SAEs, AESIs, and MAAEs.

4.4.1.2.1 Presence

An observation was considered an event if it had at least a verbatim term and was not a Grade 0 intensity event.

Grade 0 events should be included in a separate listing "Unsolicited AEs not included in the safety analysis".

4.4.1.2.2 Intensity

Intensity for unsolicited AEs will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Note: the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the Investigator (eg, swelling measurement > 0 mm but < 25 mm in adults).

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

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

For those participants receiving a non-study authorized/approved COVID-19 vaccine (eg, on Day X), the maximum intensity of unsolicited AE is analyzed as following:

- If an unsolicited AE with both time of onset and stop date before Day X, then the maximum intensity for that AE will be analyzed as collected in CRF.
- If an unsolicited AE with time of onset before Day X and the corresponding stop date is on or after Day X, then the maximum intensity for that AE will be analyzed as Missing.

4.4.1.2.3 Last Vaccination

The last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the clinical database and is calculated as follows:

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

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE provided in the clinical database and the date of last vaccination as described in Section 4.4.1.2.3:

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

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 21 days", which corresponds to AEs with a time of onset between 1 and 22 days or missing.

An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number in "Appeared after visit" or similar filed, so will be included in these tables.

Time of onset will be displayed as follows:

- D01-D04
- D05-D08
- D09-D15
- D16 or later
- Missing

Note: To further clarify the analysis,

- Any unsolicited AEs collected throughout the study (SAEs, MAAEs, or AESIs) with time of onset > 22 days after each injection will not be presented in tables of unsolicited AEs within 21 days but only in tables of SAEs, MAAEs, or AESIs.
- Any unsolicited AEs (planned to report up to 21 days) with time of onset between 1 and 22 days or missing after each injection will be presented in the tables of unsolicited AEs within 21 days.
- Any unsolicited AEs (planned to report up to 21 days) with time of onset > 22 days after each injection will not be presented in any tables but listed separately.
- Any unsolicited AEs with null (0) or negative time of onset will be excluded from the above tables and listed separately.

Main safety analysis will include only those unsolicited AEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine if applicable. Events with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.2.5 Duration

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

Duration = stop date of unsolicited AE - start date of unsolicited AE + 1

The duration should be considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

For those participants receiving a non-study authorized/approved COVID-19 vaccine (eg, on Day X), the duration is categorized as following:

- If an unsolicited AE with both time of onset and stop date before Day X, then the duration for that AE will be derived same as above.
- If an unsolicited AE with time of onset before Day X and the corresponding stop date is on or after Day X, then the duration will be derived as Missing.

Duration will be displayed by period as following:

- 1-3 days
- 4-7 days
- 8 days or more
- Missing

4.4.1.3 SAEs

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

- Within 21 days after each injection
- During the study (ie, all SAEs occurred during the entire study or the cutoff date which corresponds to the date of any interim analysis)

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

Main safety analysis will include only those SAEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. SAEs with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.4 Laboratory Test Results

Biological safety tests (biochemistry, hematology, urinalysis, and coagulation) will be performed at the local laboratory. Biological endpoints will be assessed on samples taken at screening and D09 for all participants, D30 (only applicable for Sentinel Cohort and Cohort 2), and unscheduled visits based on Investigator's judgment, in cases of abnormal safety laboratory results.

The parameters to be evaluated are detailed in Table 10.1 of the protocol.

Endpoints will be defined as either within or outside normal range. Normal ranges for each endpoint will be provided by the study center. The biological safety information will be entered by the site staff in the appropriate CRF forms along with units and normal ranges. In case of out-of-range values, specific endpoints may be rechecked, and additional biological parameters may be evaluated, based on the Investigator's judgement. This complementary safety information will also be entered by the site staff in the appropriate CRF forms along with units and normal ranges.

Any change in the testing equipment using different ranges should be reported on an ongoing basis to the Sponsor so that any value can be interpreted at a given time against the appropriate range of values.

Biological safety endpoints will be assessed on whether or not they reach the pre-defined intensity levels (Grade 1, 2, or 3) for analytes with applicable toxicity grading, as specified in the protocol. Table 10.4 of the protocol contains the pre-defined intensity scales according to which the biological safety parameters will be assessed. If at least 1 of these intensity levels is reached, the Investigator will evaluate the clinical significance of the results and report clinically significant abnormal values as AEs in the CRF.

If an endpoint reaches the pre-defined intensity threshold but is within the normal range provided by the study center, it will be treated as not reaching the intensity threshold.

4.4.1.5 Other Safety Endpoints

4.4.1.5.1 Pregnancy

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

4.4.1.5.2 Action Taken

Solicited injection site/systemic reactions after any vaccine injection(s) will be summarized by action taken.

4.4.1.5.3 Seriousness

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

4.4.1.5.4 Outcome

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

4.4.1.5.5 Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.5.6 AEs Leading to Study Discontinuation

A flag will be available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- For participants disposition: if participants did not complete the study due to AE as recorded in Completion at End of Study form
- For safety overview: if participants did not complete the study due to AE as recorded in Completion at End of Study form or had any solicited or unsolicited AEs causing study discontinuation / termination as recorded in solicited reaction or unsolicited AE forms within the time period indicated

- For summary of unsolicited AEs by system organ class (SOC) / PT: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Termination" checked that is at least Grade 1 or missing and is within the time period indicated

4.4.1.5.7 AESI

AESIs will be collected throughout the study 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 causality.

AESIs will include:

- Protocol-specified AESIs: Anaphylactic reactions, generalized convulsions, Guillain-Barré Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), thrombocytopenia, and vasculitides
- New-onset chronic medical conditions (NOCMCs)
- AESIs related to SARS-CoV-2 infection and COVID-19 disease (see Appendix 10.5 of the protocol).

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.

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

- Within 21 days after each injection
- During the study (ie, all AESIs occurred during entire the study or the cutoff date which corresponds to the date of any interim analysis)

Note: AESI with time of onset before first vaccination (negative time of onset) will not be included in analysis but will be listed separately.

Main safety analysis will include only those AESIs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. AESIs with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.5.8 MAAE

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

MAAEs will be analyzed during the following time periods:

- Within 21 days after each injection
- During the study (ie, all MAAEs occurred during entire the study or the cutoff date which corresponds to the date of any interim analysis)

Note: MAAEs with date of onset before first vaccination (negative time of onset) will not be included in analysis but will be listed separately.

Main safety analysis will include only those MAAEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. MAAEs with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.2 Immunogenicity

The following derived endpoints are applicable to the neutralizing antibody titer against the SARS-CoV-2 D614G variant and other emergent variants, and the binding antibody titers to trimerized SARS-CoV-2 S protein.

4.4.2.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantification [LLOQ] and > upper limit of quantification [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2.
- If a value is between LLOQ and ULOQ, then use the value reported.
- If a value is > ULOQ, then use ULOQ

4.4.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values as described in Section 4.4.2.1 and is computed as individual titer ratio:

- Post-vaccination value divided by baseline value

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

4.4.2.3 Seroconversion

The seroconversion endpoint is driven by both baseline and post-baseline computed values as described in Section 4.4.2.1 and a participant will have seroconverted if baseline values below LLOQ with detectable neutralization titer above assay LLOQ 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).

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

4.4.3 Additional Immunological Tests

4.4.3.1 T-Cell cytokine profile

A panel of soluble biomarkers in stimulated whole blood supernatants (TruCulture tubes) will be measured on D01, D22, and D36.

- Helper T cell type 1 (Th-1) and Helper T cell type 2 (Th-2) cytokines: Th1 cytokines include interferon-gamma (IFNg), interleukin (IL)-2, and tumor necrosis factor alpha (TNFα); Th2 cytokines include IL-4, IL-5, IL-13.
- Additionally, pro-inflammatory cytokine IL-6, regulatory cytokine IL-10, Helper T cell type 17 (Th-17) cytokine IL-17, granulocyte-macrophage-colony-stimulating factor (GM-CSF), and IL-21 will also be measured.

The list of cytokines is subject to be updated based on more information and knowledge on SARS-CoV-2 before the enrollment of participants of Cohort 2.

All cytokines will be measured in whole blood following stimulation with full length S protein, SEB + anti-CD28 (positive control) and in unstimulated whole blood (negative control).

Computed values for analysis

For each participant and each cytokine listed above, 3 measurements will be available for analysis. The 3 measurements are positive control, negative control, and spike stimulant. Each cytokine has its own LLOQ and ULOQ. Similar as described in Section 4.4.2.1, the computational rule below is applied.

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the value of ULOQ

Two subtractions will be calculated as below for each cytokine with computed values described above:

- Subtraction 1: (spike stimulant – negative control)
- Subtraction 2: (positive control – negative control)

If the value of the above subtractions is <LLOQ, then the result will be reported as LLOQ/2

Fold-rise

To derive the fold-rise of cytokines, the ratio of post-vaccination and baseline values of the corresponding subtractions above are used. Therefore, there are 2 fold-rise values for each cytokine per participant per visit:

- Value of a post-baseline visit (spike stimulant – negative control) / baseline value of (spike stimulant – negative control)
- Value of a post-baseline visit (positive control – negative control) / baseline value of (positive control – negative control)

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

Th-1/Th-2 ratios:

1. IFNg/IL-4
2. IFNg/IL5
3. IFNg/IL-13
4. IL-2/IL-4
5. IL-2/IL-5
6. IL-2/IL-13
7. TNFa/IL-4
8. TNFa/IL-5
9. TNFa/IL-13

The ratios above are based on fold-rise. For each cytokine, there are 2 Th-1/Th-2 ratios, one for each subtraction above. The ratio based on subtraction of spike stimulant – negative control will be used as main supportive information for Th1/Th2 results. Among all ratios listed, IFNg/IL-4 is the main Th-1/Th-2 ratio for characterizing Helper T cell polarization.

4.4.3.2 Memory B cells

Spike-Specific IgG and IgA Memory B cells will be quantified in peripheral blood mononuclear cells (PBMCs) at D01 (pre-vaccination) and at D112 (post-vaccination) using a fluorescent immunospot (FluoroSpot) assay. Both number of Spike-Specific IgG and IgA Memory B cells and number of total IgG and IgA Memory B cells are measured in Antibody Secreting Cells (ASC)/10^6PBMCs. Proportion of Spike-Specific IgG and IgA Memory B cells in % will be calculated as follows: (number of Spike-Specific IgG and IgA Memory B cells ASC/10^6PBMCs / number of total IgG and IgA Memory B cells ASC/10^6PBMCs)* 100.

4.4.4 Efficacy

The efficacy endpoints are the virologically-confirmed COVID-19-like illness and serologic SARS-CoV-2 infection.

Virologically-confirmed COVID-19-like illness

Virologically-confirmed COVID-19-like illness is 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, which is defined in the protocol Section 8.2.2.1.

Serologically-confirmed SARS-CoV-2 infection

Serologically-confirmed SARS-CoV-2 infection is 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).

4.4.5 Derived Other Variables

4.4.5.1 Age for Demographics

The age of a participant in years in the study is the calendar age in years at the time of inclusion and will be analyzed as collected in CRF.

Age group

The calendar age will be used for age sub-groups definition. The age group of a participant in the study will be based on the calendar age as follows:

"18 to 49 years" means from the day of the 18th birthday to the day before the 50th birthday.

"Over 50 years" means from the day of the 50th birthday onwards, with no upper age limit.

If only year of birth is collected, use the calculated age in years to generate age group.

4.4.5.2 Duration of the Study

The duration of the study is computed in days as follows:

- Maximum (date of last visit, date of termination, date of last contact) – minimum (date of V01) +1

4.4.5.3 Participant Duration

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

Maximum (Visit dates, Termination date, contact dates) – V01 date + 1

5 Statistical Methods and Determination of Sample Size

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

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

For descriptive purposes, the following statistics will be presented as shown in Table 5.1.

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of participants. Percentage of participants and 95% CI.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs]) of participants. Unsolicited: Number and percentage (95% CIs) of participants, and number of events.
Immunogenicity results	**Categorical data (seroconversion, 2 fold-rise, 4 fold-rise)**	Number and percentage (95% CIs) of participants.
	Continuous data (titer / data)	Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).
Efficacy results	**Categorical data**	Number and percentage (95% CIs) of participants.

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (4), ie, using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log_{10} transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

5.1 Statistical Methods

Safety, immunogenicity, and efficacy analysis will be undertaken including those data collected before the date of receiving an authorized/approved COVID-19 vaccine. Those data collected on or after receiving an authorized/approved COVID-19 vaccine will be listed separately.

For those participants who did not receive an authorized/approved COVID-19 vaccine outside the study, immunogenicity data collected until the last scheduled/unscheduled study visit will be used for analysis. Rules about how to handle unscheduled visit are detailed in Table 5.2. Safety data collected until the last phone contact will be used for analysis if participants did not receive an authorized/approved COVID-19 vaccine outside the study

Safety analyses will be conducted based on two populations: *i*) participants in the Full Enrollment Cohort (Cohort 1 and 2) only, and *ii*) all participants in the Full Enrollment Cohort and Sentinel Cohort, if necessary. Immunogenicity analyses and efficacy analyses will be conducted based on the combined population (Full Enrollment Cohort + Sentinel Cohort) only, in which the same

dose-level group in Sentinel Cohort and Full Enrollment Cohort will be pooled. Subgroup analyses will be performed by age-group.

5.1.1 Hypotheses and Statistical Methods for Primary Safety Objective

5.1.1.1 Primary Safety Hypotheses

No hypotheses were tested.

5.1.1.2 Statistical Methods for Primary Safety Objective

The following safety parameters will be used for the evaluation of safety. Additional parameters may be displayed as appropriate.

Solicited Reactions

Number and percentage of participants with:

- Presence of solicited injection site reactions and systemic reactions occurring up to 7 days after injection
- Each solicited reaction according to time of onset, maximum intensity, and number of days of occurrence over the solicited period

Unsolicited Events and Reactions

Number and percentage of participants with:

- Any unsolicited immediate systemic event in the 30 minutes after injection
- Any unsolicited event and reaction (using the current MedDRA version) 21 days after injection
- Any unsolicited event/reaction according to time of onset, maximum intensity, and duration

SAEs

Number and percentage of participants with:

- Any SAE within 21 days after injection and throughout the entire study according to SOC and PT, seriousness, and outcome

AESIs

Number and percentage of participants with:

- Any AESI within 21 days after injection and throughout the entire study according to SOC and PT, seriousness, and outcome

MAAEs

Number and percentage of participants with:

- Presence of MAAEs within 21 days after injection and throughout the entire study

Laboratory tests

- Presence of out-of-range biological test results up to 8 days post-last dose (ie, up to D09 for Cohort 1 and up to D30 for Sentinel Cohort and Cohort 2)
- Summary of toxicity grade shift from baseline

For descriptive purposes, the statistics presented in Table 5.1 will be produced for the above safety parameters for each intervention group and each age group. The same dose-level group in Sentinel Cohort and Cohort 2 will also be pooled for analysis.

Harm analysis

Harm analysis assessed based on split of COVID-19 case will be assessed based on Safety Analysis Set (SafAS) at the time of the final analysis. Participants will be analyzed according to the study intervention they received. For the assessment, all dose-level arms will be pooled, and all placebo arms will be pooled as well.

The assessment for COVID-19 will be implemented separately using a one-sided conditional exact binomial test of H0: p ≤ "number of participants in the pooled mRNA vaccine arm"/ "total number of participants" versus H1: p > "number of participants in the pooled mRNA vaccine arm"/ "total number of participants", where p is the binomial probability that a case participant is assigned to the pooled mRNA 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%.

5.1.1.3 Primary Immunogenicity Hypotheses

No hypotheses will be tested.

5.1.1.4 Statistical Methods for Primary Immunogenicity Objective

The primary endpoints for the evaluation of immunogenicity are based on pseudovirus neutralizing antibody titers against D614 variant, which will be measured with the pseudovirus neutralization assay. The statistical analyses will be performed for the following primary endpoints below in each age and intervention group:

1. Neutralizing antibody titer on D01, D22, and D36
2. Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36
3. 2-fold and 4-fold rise in serum neutralization titer relative to D01 at D22, and D36
4. Occurrence of neutralizing antibody seroconversion, defined as baseline values below LLOQ with detectable neutralization titer above assay LLOQ at D22 and D36

The 95% 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. Additional parameters may be displayed as appropriate.

For descriptive purposes, the statistics presented in Table 5.1 will be produced for each intervention group and each age group. The same dose-level group in Sentinel Cohort and Cohort 2 will be pooled for analysis.

Additionally, to evaluate independent determinants of primary immunogenicity endpoints, regression models may be constructed for log transformed titers and occurrence of 4-fold rise in serum neutralization titer relative to D01 at D22 for Cohort 1 and D36 for Sentinel Cohort and Cohort 2. When the outcome/dependent variable is a continuous numerical variable, linear model may be utilized; when the outcome/dependent variable is a categorical variable, logistic regression models may be utilized. Explanatory/independent variables inserted in these models would include age group (18-49 years, ≥ 50 years) and the injection schedule (1-injection, 2-injections). Models evaluating antibody titers or rates may include also an explanatory variable corresponding to the antigen dose level (ultra-low-dose, low-dose, medium-dose) when more than 1 dose level is to be used for the Full enrollment Cohort. Multiplicative interaction terms will be included in expanded models to assess for evidence of effect modification. Non-significant interaction terms with critical value < 0.05 can be removed from the models.

As the development of the mRNA COVID-19 vaccine has been suspended, the between groups ratios of GMTs and seroconversion rates differences planned at the time of the protocol will not be performed.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Secondary Immunogenicity Hypotheses

No hypotheses were tested.

5.1.2.2 Statistical Methods for Secondary Immunogenicity Objectives

The secondary endpoints for the evaluation of immunogenicity are presented in Table 3.1 of the protocol. The 95% CIs for the anti-S antibody concentration and anti-S antibody concentration 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. Additional parameters may be displayed as appropriate.

For descriptive purposes, the statistics presented in Table 5.1 will be produced.

As the development of the mRNA COVID-19 vaccine has been suspended, the between groups ratios of anti-S antibody concentrations and seroconversion rates differences planned at the time of the protocol will not be performed.

Handling unscheduled serology samples

As scheduled visits after D22 or D36 were no longer required after enrollment and vaccination was interrupted, it is expected that a very limited number of serology samples will be within the planned time window 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). Nevertheless, a number of serology samples were obtained at unscheduled visits from participants prior to receipt of an authorized/approved COVID-19 vaccine or unblinding. To

assess the long-term immunogenicity, the unscheduled visit from each participant will need to be associated with one of the protocol-defined schedule visit, based on the rules detailed in Table 5.2.

Table 5.2: Derivation rules to map unscheduled visits to protocol-defined visits

Injection scheme	Analysis visit	Protocol-defined timelines	Derivation rule for unscheduled visits
1 injection	V02	D09 (V01+8 days) [+2 days]	1 ≤ Unscheduled visit date –V01 date ≤ 15
	V03	D22 (V01+21 days) [+7 days]	16 ≤ Unscheduled visit date –V01 date ≤ 31
	V04	D36 (V01+35 days) [+7 days]	32 ≤ Unscheduled visit date –V01 date ≤ 66
	V05	D91 (V01+90 days) [+7 days]	67 ≤ Unscheduled visit date –V01 date ≤ 138
	V06	D181 (V01+180 days) [+14 days]	139 ≤ Unscheduled visit date –V01 date ≤ 279
	V07	D366 (V01+365 days) [+14 days]	280 ≤ Unscheduled visit date –V01 date
2 Injections	V04	D30 (V03+8 days) [+2 days]	1 ≤ Unscheduled visit date – V03 date ≤ 12
	V05	D36 (V03+14 days) [+7 days]	13 ≤ Unscheduled visit date – V03 date ≤ 55
	V06	D112 (V03+90 days) [+7 days]	56 ≤ Unscheduled visit date – V03 date ≤ 138
	V07	D202 (V03+180 days) [+14 days]	139 ≤ Unscheduled visit date – V03 date ≤ 279
	V08	D387 (V03+365 days) [+14 days]	280 ≤ Unscheduled visit date – V03 date

5.1.2.3 Secondary Efficacy Hypotheses

No hypotheses were tested.

5.1.2.4 Statistical Methods for Secondary Efficacy Objectives

The efficacy profile of the study vaccine candidate was planned to be investigated with collected COVID-19 cases of efficacy endpoint including virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection. However, as the development of the mRNA COVID-19 vaccine has been suspended, analyses of correlated of risk and of vaccine efficacy will not be performed.

5.1.3 Statistical Methods for Exploratory Objectives

No hypotheses will be tested.

For descriptive purposes, the statistics presented in Table 5.1 will be produced.

Exploratory Immunogenicity Objectives

Ratio between pseudovirus neutralizing antibody titer and binding antibody (ELISA) concentration will be calculated and provided with 95% CI by study intervention groups. Analyses will be conducted on overall population and by age group.

Last available pseudovirus neutralizing antibody titer and binding antibody (ELISA) concentration before infection will be described with 95% CI in aggregated mRNA vaccine group

and aggregated placebo group among the virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection.

Antibodies titers measured using a live virus neutralization assay or other assays and antibody against other emergent variants (eg, B.1.351, B.1.1.7, P.1) might also be summarized in terms of GMTs, fold-rise, and percent of participants with ≥ 2-fold rise and ≥ 4-fold rise titers and their corresponding 95% CI at each testing timepoints (D01, D36, and other timepoints), if applicable.

Post-vaccination antibody titers for the different study intervention groups may be compared with human convalescent sera antibody titers, conditional to convalescent sample availability.

T-Cell cytokine profile

For descriptive purposes, the statistics presented in Table 5.1 will be produced for:

- the levels of each cytokine measured at D01, D22, and D36
- the fold-rise of each cytokine measured at D22 and D36 against baseline (D01)
- the Th-1/Th-2 ratios of the fold-rises at D22, D36 against baseline (D01)

Memory B cells

The descriptive statistics presented in Table 5.1 will be produced for the memory B cells measured at D01 (pre-vaccination) and at D112 (post-vaccination), the proportion of antigen-specific ASC, and their fold-rises at D112 relative to D01.

5.2 Analysis Sets

Five main analysis sets were originally defined in the protocol: the PPAS, the Per-Protocol Analysis Set for immunogenicity (PPAS-IAS), the Per-Protocol Analysis Set for AIT (PPAS-AIT), the Full Analysis Set (FAS), and the SafAS. An additional Analysis Set of "modified FAS" is defined in this version of SAP. SafAS1 and SafAS2 will also be used for safety post dose 1 or post dose 2.

5.2.1 Full Analysis Set

Subset of randomized participants who received at least 1 injection of the study intervention. Participants will be analysed according to the intervention group to which they were randomized.

5.2.2 Safety Analysis Set

The SafAS is defined as subset of randomized participants who have received at least 1 injection of study intervention. All participants will be analyzed after any dose according to the intervention received at the 1st dose.

The SafAS1 and SafAS2 are defined as subsets of randomized participants who have received the 1st or the 2nd injection of study intervention respectively. All participants will be analyzed after each dose according to the intervention they received.

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

5.2.3 Per-Protocol Analysis Set

Subset of the FAS. Participants presenting with at least one of the following conditions will be excluded from the PPAS:

- Participant did not meet all protocol-specified inclusion criteria or met at least one 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 as defined in the protocol visits.
- Participant receives an authorized/approved COVID-19 vaccine prior to D22 (Cohort 1) or D36 (Sentinel Cohort and Cohort 2).
- Participant with positive test results (≥ LLOQ) in the pseudovirus neutralization test* at baseline.

*Only SARS-CoV-2 D614G variant will be considered.

The above conditions leading to exclusion from the PPAS may be detailed and completed if necessary, following the data review. In any case, if PPAS definition is modified, the PPAS definition will be finalized before the database lock and documented in an SAP update.

5.2.3.1 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.

For participants with just a few expected post-dose serology samples outside the proper time window or without a valid test result, participants will be kept in PPAS-IAS and only samples within time window and with valid result will be included in immunogenicity analyses.

5.2.3.2 Per-Protocol Analysis Set for AIT subset (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.

5.2.4 Other Analysis Sets

Enrolled participants

All participants with a dose-level group that has been allocated by interactive response system (IRT).

Randomized participants

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

Participants with data in CRF

Participants with data in CRF are participants for whom data were recorded at a visit (except screening).

Modified FAS (mFAS)

Subset of FAS that excludes participants with positive pseudovirus neutralization test results against SARS-CoV-2 D614G variant at baseline (D01).

5.2.5 Populations Used in Analyses

Participants' disposition, demographics, baseline characteristics and exposure will be summarized by planned intervention group for all screened participants or Enrolled participants.

The primary safety analysis will be performed on the SafAS, SafAS1, and SafAS2 by injection group according to the vaccine received.

The primary immunogenicity analyses, the secondary immunogenicity analyses, and the exploratory immunogenicity analyses will be performed on the mFAS by injection group as actually received. This is due to a high rate of protocol deviations and dosing errors found in the preliminary analysis for sentinel cohort.

The secondary efficacy analysis will also be performed on the mFAS by injection group as actually received.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

Generally, no replacement will be done. However, imputations may be done for a limited number of scenarios, some of which are described in this section.

5.3.1.1 Immediate

Unsolicited systemic AEs with a missing response to the "Immediate" field will be assumed to have occurred within the 30-minute surveillance period.

5.3.1.2 Causality

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions. Missing causality for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

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

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.2 Immunogenicity

No test or search for outliers will be performed.

5.3.3 Laboratory Safety

No imputation of missing values and no search for outliers will be performed.
For the computation of descriptive statistics, a value reported as:

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

If a participant has a missing baseline then the data for this participant will be included in the category "missing at baseline" in the table taking into account the baseline status.

5.3.4 Additional Immunological Tests

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ , then use the value
- If a value is ≥ ULOQ, then use the value of ULOQ

5.3.5 Efficacy

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

5.4 Interim / Preliminary Analysis

A preliminary interim analysis was performed on safety and immunogenicity including pseudovirus neutralizing antibody and binding antibody (ELISA) data collected up to D43 for participants enrolled into the Sentinel Cohorts. Database was cleaned with a partial database lock

conducted. After that, the clinical team decided to terminate further vaccination and enrollment, and all enrolled participants were to be unblinded, thus allowing each of them to make an informed decision as to whether they want to receive an authorized COVID-19 vaccine.

The remaining interim analyses that have been specified in protocol will no longer be performed as the development of the mRNA COVID-19 has been discontinued and the study enrollment and vaccination has been interrupted.

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 of the protocol for Sentinel Cohort dose escalation, Section 8.4.2 of the protocol for CS-ESDR details, and Section 8.4.3 of the protocol for halting rules for the entire study).

5.5 Determination of Sample Size and Power Calculation

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

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-level, 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. A subset of up to 77 randomly selected participants in Cohort 2 will be included in an AIT subset. Please refer to Table 4.2 and Table 4.3 of the protocol for the planned sample size in Sentinel Cohort and Full Enrollment Cohort.

5.6 Data Review for Statistical Purposes

A review of the data will be led by data management before database lock. This review of the data included statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The content of the current SAP is based on protocol v3.0 and the following modifications.

When conducting the planned preliminary interim analysis, as the sensitivity of the rapid diagnostic test (RDT), used to assess seropositivity at screening, was low, an ad hoc analysis set "mFAS" was defined as a subset of the FAS that excludes participants with positive pseudovirus neutralization test results against SARS-CoV-2 D614G variant at baseline. In addition, due to 8 participants in the Sentinel Cohort with dosing errors related protocol deviations, immunogenicity analyses were performed using "mFAS" according to the study intervention participants actually received. The "mFAS" by injection group will also be used in the final analysis.

After the planned preliminary interim of the Sentinel Cohort participants, a decision to discontinue the development of the mRNA COVID-19 vaccine was made. On September 27, 2021, all Investigators were informed to terminate further vaccinations and enrollment. All

enrolled participants were to be unblinded to allow them to make their decision to receive an authorized COVID-19 vaccine. All clinical sites were to contact participants to inform them of the discontinuation of further study vaccinations, told what intervention they received and invited to come in for an unscheduled visit for counseling to answer any questions about the study, to discuss available options for receipt of an approved /authorized COVID vaccination, and were requested to provide unscheduled blood draw for serological assessment (UBXX). Participants were informed that additional D22 or D36 blood draws for serological assessment would be appreciated but are not mandatory. No protocol defined schedule visits or blood draws at timepoints later than D36 were required. Monitoring for SAEs, AESIs, medically attended AEs, and pregnancy and collection of influenza and COVID-19 vaccines were continued with safety calls. On March 15, 2022, after concurrence from regulatory authorities, Investigators were notified of the decision to end the study at the 6-month safety follow-up instead of 12-month follow-up.

As the further development of the mRNA COVID-19 vaccine was terminated and as mentioned above in Section 5.4, interim analyses initially planned in the protocol will not be performed. The final analysis will be conducted in an unblinded manner.

In addition, the following analyses planned at the time of the protocol or previous version of SAPs will not be performed:

- Between groups ratios of neutralizing Ab GMTs and between group seroconversion rates differences
- Between groups ratios of anti-S antibody concentrations and between group seroconversion rates differences
- Correlated of risk and of vaccine efficacy
- Complementary analysis and sensitive analysis on immunogenicity data and safety data
- Safety and immunogenicity analyses by aggregated groups

Detailed analyses can be found in the SAP document of Tables, Listings and Figures.

6 References List

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