ModernaTX, Inc.

Protocol mRNA-1273-P206

A Phase 2, Two-Part Study (Open-Label [Part 1] Followed by Observer-Blind/Randomized [Part 2]) to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 Vaccine in Participants Aged 12 Weeks to < 6 Months

Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Definition
AB	antibody
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
BMI	body mass index
bAb	binding antibody
BLA	Biologics License Application
CI	confidence interval
CDC	United States Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
GLSM	geometric least squares mean
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
IP	investigational product
IRT	interactive response technology
IST	internal safety team
LAR	legally authorized representative
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified Intent-to-Treat
mITT-1	modified Intent-to-Treat-1
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PP	per-protocol
PPIS	Per-Protocol Immunogenicity Subset
PPIS-Neg	Per-Protocol Immunogenicity Subset - Negative
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
SRR	seroresponse rate
Study P301	Study mRNA-1273-P301; NCT04470427
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
US	United States
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P206, is based on the most recent approved clinical study protocol (CSP), Original Version, dated 17-Jun-2022 and the most recent approved electronic case report form (eCRF) Version 4.004, dated 09-Mar-2023.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 8) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P206 is a Phase 2, two-part, open-label in Part 1 and observer-blind, randomized, placebo-controlled in Part 2 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273.214 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in infants aged 12 weeks to < 6 months.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, tolerability, reactogenicity, and effectiveness data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, subject and participant are used interchangeably; injection of investigational product (IP), injection, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objective

The primary objectives for Part 1 are the following:

- To evaluate the safety and reactogenicity of 2 dose levels (5 µg and 10 µg) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months.

The primary objectives for Part 2 are the following:

- To evaluate the safety and reactogenicity of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months.
- To infer the effectiveness of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months.

2.2. Secondary Objectives

The secondary objectives for Part 1 are the following:

- To evaluate the immunogenicity of 2 dose levels (5 µg and 10 µg) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months.

The secondary objectives for Part 2 are the following:

- To evaluate the immune response against SARS-CoV-2 variants of concern (VOC) (Omicron) elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273 primary series (100 µg, 2 doses 28 days apart).
- To evaluate the immune response against SARS-CoV-2 original strain elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273 primary series (100 µg, 2 doses 28 days apart).

2.3. Exploratory Objectives

There are no exploratory objectives for Part 1.

For Part 2, the exploratory objectives are the following:

- To evaluate the incidence of coronavirus disease 2019 (COVID-19) after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart.
- To evaluate the incidence of SARS-CoV-2 infection after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart.

- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart.
- To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection.
- To evaluate immune response elicited by the primary series of mRNA-1273.214 against variant(s) of interest.

3. Study Endpoints

3.1. Primary Endpoints

The primary safety objective for Part 1 and Part 2 will be evaluated by the following safety endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection
- Unsolicited adverse events (AEs) through 28 days after each injection
- Medically attended AEs (MAAEs) throughout the entire study period
- Serious AEs (SAEs) throughout the entire study period
- AEs of special interest (AESIs) throughout the entire study period
- AEs leading to discontinuation from study participation postdose throughout the entire study period

The primary immunogenicity objective to infer effectiveness of the mRNA-1273.214 vaccine for Part 2 will be evaluated by:

- Co-primary Endpoint: geometric mean (GM) value of antibodies (Ab) against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult participants at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 (100 μg, 2 doses 28 days apart) primary series
- Co-primary Endpoint: seroresponse rate (SRR) against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult participants at Day 57 (28 days after the second dose) in Study

mRNA-1273-P301 dosed with mRNA-1273 (100 µg, 2 doses 28 days apart) primary series

3.2. Secondary Endpoints

The secondary objective in Part 1 will be evaluated by the following endpoint:

- GM value of antibodies against SARS-CoV-2 VOC (Omicron) at 28 days after second dose

The secondary objectives in Part 2 will be evaluated by the following endpoints:

- GM value of antibodies and SRR against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214, compared with GM value and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series
- GM value of antibodies and SRR against SARS-CoV-2 original strain at 28 days after the second dose of mRNA-1273.214, compared with GM value and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series

3.3. Exploratory Endpoints

The exploratory endpoints for Part 2 are the following:

- The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on CDC case definition
- The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or reverse transcription polymerase chain reaction [RT-PCR]) postbaseline SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:
    - Binding antibody (bAb) level against SARS-CoV-2 nucleocapsid protein negative at Day 1, that becomes positive (as measured by ligand-binding assay) postbaseline, OR
    - Positive RT-PCR postbaseline
- The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by ligand-binding assay) postbaseline

in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms

- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
- GM, SRR, and geometric mean fold rise (GMFR) of Ab against variant(s) of interest

4. Study Design

4.1. Overall Study Design

This is a Phase 2, two-part, open-label in Part 1 and observer-blind, randomized, placebo-controlled in Part 2 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273.214 SARS-CoV-2 vaccine in infants aged 12 weeks to < 6 months. The study will be conducted at multiple sites in the United States (US) enrolling approximately 700 participants. Participants who withdraw or are withdrawn from the study will not be replaced.

The study will be conducted in 2 parts. Part 1 will consist of Arm 1 and Arm 2 that will enroll sequentially, i.e., Arm 1 will begin enrollment and the periodic safety review will determine whether Arm 2 can begin enrollment. A total of 100 participants (50 participants in each arm) will be enrolled in Part 1 and will receive 5 µg of mRNA-1273.214 in Arm 1 and 10 µg of mRNA-1273.214 in Arm 2. While participants may be screened up to 1 month prior to dosing, they must be 12 weeks completed age at the time of receipt of first dose. Arm 1 will start with 2 doses of 5 µg (sentinel dosing) administered 8 weeks apart of up to 4 participants. An internal safety team (IST) will review safety data after Dose 1 (1 week after Dose 1 of mRNA-1273.214) and provide a recommendation to further dose participants. Once safety and tolerability after Dose 1 have been reviewed by the IST, Arm 1 will continue enrollment for a total of 50 participants.

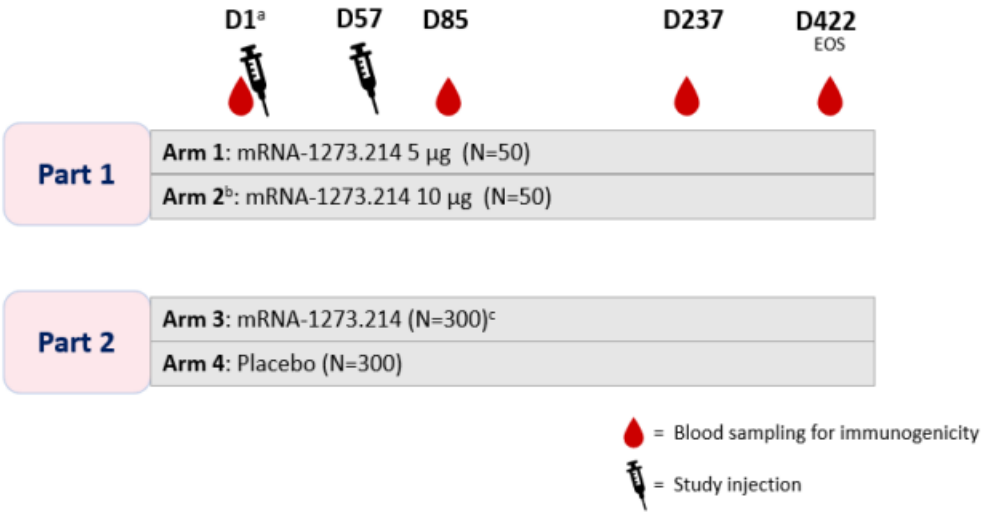
The IST will reconvene once 25 participants in Arm 1 reach Day 64 (1 week after Dose 2 of 5 µg administered 8 weeks apart). If no safety concerns are identified after IST review in Arm 1, Arm 2 will begin enrollment and participants will receive 2 doses of 10 µg of mRNA-1273.214 administered 8 weeks apart. Similar to Arm 1, safety and tolerability will be reviewed by the IST after 4 participants have received Dose 1 (1 week after Dose 1 of mRNA-1273.214), and again when 25 participants reach Day 64, and provide a recommendation for continuing dosing and enrollment at each review. Arm 2 will enroll a

total of 50 participants. The immunogenicity and safety analysis will be conducted after all treated participants in both Arms 1 and 2 reach Day 85 (28 days from second dose). The results from Part 1 will determine the dose level for Part 2, which will be blinded and randomized.

Part 2 of the study will consist of 2 groups (Arm 3 and Arm 4). In Part 2, a total of approximately 600 participants will be randomly assigned to receive mRNA-1273.214 (Arm 3) or placebo (Arm 4) in a 1:1 ratio (n = 300 per arm). Part 2 will utilize the mRNA-1273.214 dose selected in Part 1. Study vaccine will be administered nonconcomitantly to routine pediatric vaccinations. Participants will be followed for approximately 12 months after completion of the primary series.

The study schema is illustrated in Figure 1.

Figure 1 Study Schema



Abbreviations: D = Day; EOS = end of study; IST = internal safety team; mRNA = messenger RNA; N = number of participants.

a. Participant must be 12 weeks old at Day 1.
b. Arm 2 will begin enrollment after IST review of safety data collected from 25 participants in Arm 1 who have reached Day 64 (1 week after second dose of 5 µg).
c. At selected dose level from Part 1.

4.2. Statistical Hypotheses

Part 1:

There is no statistical hypothesis to be tested in Part 1.

Part 2:

Primary Hypotheses:

1) HA^1: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.667).

2) HA^2: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

Secondary Hypotheses:

3) HA^3: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a superiority margin of > 1-fold (lower bound of CI for GMR > 1).

4) HA^4: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a superiority margin of > 0% (lower bound of CI for SRR > 0%).

5) HA^5: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is "super" superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a "super" superiority margin of > 1.5-fold (lower bound of CI for GMR > 1.5).

6) HA^6: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is "super" superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a "super" superiority margin of > 10% (lower bound of CI for SRR > 10%).

7) HA^7: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on GMR with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.667).

8) HA^8: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 μg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on difference in SRR with a noninferiority margin of < 5% (lower bound of CI for SRR > − 5%).

9) HA^9: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 μg mRNA-1273 in adults based on GMR against the SARS-CoV-2 original strain with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.667).

10) HA^{10}: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 μg mRNA-1273 against the original strain in adults based on difference in SRR against the SARS-CoV-2 original strain with a noninferiority margin of < 5% (lower bound of CI for SRR > − 5%).

4.3. Sample Size and Power

In Part 2, approximately 600 infant participants 12 weeks to < 6 months of age will be enrolled at the dose level selected for Part 2, with an mRNA-1273.214 to placebo ratio of 1:1. Assuming 10% to 15% participants are not negative SARS-CoV-2 status at baseline, it is estimated that there will be a minimum of approximately 250 evaluable participants in the mRNA-1273.214 arm eligible for immunogenicity analyses.

The sample size of approximately 300 infant participants in the mRNA-1273.214 arm in Part 2 is considered to be sufficient to support a safety assessment. There is at least 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% in this group.

The sample size calculation for each of the 2 primary noninferiority hypothesis tests (H_A^1 and H_A^2) was performed, and the larger sample size was chosen for the study.

- With approximately 250 evaluable participants receiving mRNA-1273.214 in the Per-Protocol Immunogenicity Subset - Negative (PPIS-Neg) in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority of the immune response against Omicron variant, as measured by the geometric mean concentration (GMC) or GM level, in infant population at a 2-sided alpha of 0.05, compared with that in adults (≥ 18 years of age) in Study mRNA-1273-P301 receiving mRNA-1273, assuming an underlying geometric mean ratio (GMR) (which is calculated as ratio of GMC or

GM level) value of 1 and the standard deviation of the natural log-transformed concentration/level is assumed to be 1.0, and a noninferiority margin of > 0.667.

- With approximately 250 evaluable participants receiving mRNA-1273.214 in the PPIS-Neg in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority of the immune response against Omicron variant as measured by SRR in infants at a 2-sided alpha of 0.05, compared with SRR against Omicron variant in adults ≥ 18 years of age in Study mRNA-1273-P301 receiving mRNA-1273, assuming SRR of 60% to 70% in Study mRNA-1273-P301, true SRR improvement of 10% in infants from Study mRNA-1273-P206 compared with adults from Study mRNA-1273-P301, and a noninferiority margin of 5%.

4.4. Randomization

Random assignment of participants in Part 2 of the study will use a centralized interactive response technology (IRT), in accordance with pre-generated randomization schedules. Approximately 600 participants will be randomized in a 1:1 ratio to the mRNA-1273.214 arm or placebo arm (n = approximately 300 participants in each group).

4.5. Blinding and Unblinding

This study is conducted in two parts. Part 1 of this study will be open-label and blinding procedures will not be applicable.

Part 2 of this study will be conducted in an observer-blind manner. The investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with certain exceptions (please refer to Section 9.1 of the protocol for details).

At the time of interim analysis, only pre-identified Sponsor and unblinded Contract Research Organization (CRO) team members as specified in the study Data Blinding Plan will be unblinded to review treatment level results and individual listings. Please also refer to Section 6.6. Study sites will remain blinded to individual treatment assignments until the end of the study.

If a COVID-19 vaccine (mRNA-1273 or other) is authorized or licensed for infants, parent(s)/legally authorized representative(s) (LAR) of eligible study participants (by virtue of their age) will be offered the opportunity to unblind via a phone call and learn what treatment the participant received, ideally after they have reached at least Day 85 in the

study. Participants who have received mRNA-1273.214 will continue in the study and will be followed per protocol. If a participant previously received placebo, then their parent(s)/LAR(s) will be advised to discuss with the participant's primary care physician and follow current Centers for Disease Control and Prevention (CDC) recommendations regarding COVID-19 immunization. If a participant who received placebo in the study chooses to receive a non-study COVID-19 vaccine, they will be withdrawn from the study.

5. Analysis Populations

The following analysis sets are defined for Part 1 open-label phase and Part 2 blinded phase:

- Randomization Set
- Full Analysis Set (FAS)
- Modified Intent-to-Treat (mITT) Set
- Modified Intent-to-Treat-1 (mITT-1) Set
- Per-Protocol (PP) Set
- Immunogenicity Set
- Per-Protocol Immunogenicity Subset (PPIS)
- PPIS-Neg Set
- Safety Set
- Solicited Safety Set

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized in Part 2 of the study, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2. Full Analysis Set

The Full Analysis Set (FAS) for Part 1 consists of all enrolled participants who receive at least 1 injection of IP, and the FAS for Part 2 consists of all randomized participants who receive at least 1 injection of IP. Participants will be analyzed according to the treatment group for the treatment they actually received in Part 1 and will be analyzed according to the treatment group to which they were randomized in Part 2.

5.3. Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) Set consists of all participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline.

Participants in Part 2 will be analyzed according to the treatment group to which they were randomized.

5.4. Modified Intent-to-Treat-1 (mITT-1) Set

The Modified Intent-to-Treat-1 (mITT-1) Set consists of all participants in the mITT Set excluding those who received wrong treatment (i.e., at least one dose received that is not as randomized or planned).

Participants in Part 2 will be analyzed according to the treatment group to which they were randomized.

5.5. Per-Protocol (PP) Set

The Per-protocol (PP) Set consists of all participants in the FAS who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Had no major protocol deviations that impact key or critical data

c) Had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline

The PP Set will be used as the primary analysis population in the efficacy analyses unless otherwise specified. Participants will be analyzed according to the treatment group to which they were randomized in Part 2.

5.6. Immunogenicity Set

Immunogenicity Set (IS) consists of all participants in the FAS who provide immunogenicity samples.

5.7. Per-Protocol Immunogenicity Subset (PPIS)

PPIS consists of all participants in Immunogenicity Subset who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Complied with the immunogenicity testing schedule

c) Had baseline (Day 1) and Day 85 Ab assessments for the analysis endpoint

d) Had no major protocol deviations that impact key or critical data

The PPIS will be used for sensitivity analyses or supportive analysis of immunogenicity data. Participants will be analyzed according to the treatment group which they actually received in Part 1 and to which they were randomized in Part 2.

5.8. Per-Protocol Immunogenicity Subset - Negative

Per-Protocol Immunogenicity Set - Negative (PPIS-Neg) includes participants in the PPIS who are SARS-CoV-2 negative (no serologic or virologic evidence of prior SARS-CoV-2 infection) before receiving the first dose of IP.

PPIS-Neg will serve as the primary population for the analysis of immunogenicity data.

5.9. Safety Set

The Safety Set consists of all enrolled (Part 1) or randomized (Part 2) participants who received at least one dose of IP. The Safety Set will be used for analysis of safety except for the solicited ARs. In addition, the following Safety Set is defined for each injection separately. The First Injection Safety Set consists of all subjects in the Safety Set who have received the first study injection. The Second Injection Safety Set consists of all subjects in the Safety Set who have received the second study injection. Participants will be included in the vaccination group corresponding to the vaccination they actually received. For a participant who was randomized to placebo in Part 2 but received any dose of mRNA-1273.214 at any injection, the participant will be included in the mRNA-1273.214 group in the Safety Set.

5.10. Solicited Safety Set

The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one postbaseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be

included in the vaccination group corresponding to the study injection they actually received. In addition, the following Solicited Safety Set is defined for each injection separately.

The First Injection Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the first study injection and have contributed any solicited AR data from the time of first study injection through the following 6 days.

The Second Injection Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the second study injection and have contributed any solicited AR data from the time of second study injection through the following 6 days. Participants will be analyzed according to the vaccination group a participant received, rather than the vaccination group to which the subject was randomized. A participant who was randomized to placebo but received any dose of mRNA-1273.214 at any injection will be included in the mRNA-1273.214 group in the Solicited Safety Set.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in Appendix E for Part 1 and 2.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

Categorical variables will be summarized using counts and percentages. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that vaccination group within the analysis set of interest, unless otherwise specified.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP. For immunogenicity tests and nasal swab tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP (Day 1) prior to the first dose of IP.

Baseline SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

Positive SARS-CoV-2 status at Baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Negative status at Baseline is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Study day relative to the first injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection will be calculated as: date of assessment/event – date of the first injection + 1

Study day relative to the most recent injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;

c) study day on or after the date of the second injection will be calculated as: date of assessment/event – date of the second injection + 1; if study day is on the same day as the second injection, date and time will be compared with the second injection date and time. If time is prior to the time of second injection, then study day is calculated as: date of assessment/event – date of the first injection + 1; If it is after the time of second injection or the time is missing or not available then study day is calculated as: date of assessment/event – date of the second injection + 1.

For calculation regarding antibody levels/concentrations, antibody values reported as below LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ if actual values are not available, and actual values will be used if available. Missing results will not be imputed.

The following **analysis periods or stages for safety analyses** will be used in this study:

- Up to 28 days after any vaccination: this stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.
- Overall period (throughout the study): this analysis period starts at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following vaccination groups will be used for summary purposes:

- Part 1, Open-Label Phase:
  - mRNA-1273.214 5 µg
  - mRNA-1273.214 10 µg
  - mRNA-1273.214 Total
- Part 2, Blinded Phase:

  Treatment in Part 2 will be the selected dose level from Part 1 or Placebo
  - mRNA-1273.214 5 µg, or
  - mRNA-1273.214 10 µg

  And
  - Placebo

Subjects who received at least one dose of mRNA-1273.214 in Part 2 will be included in the mRNA-1273.214 selected dose level group (as actual treatment) in Part 2 in the safety and immunogenicity analyses.

External comparator:

- Comparator: mRNA-1273 100 µg primary series (from study P301 in young adult participants (18-25 years) who received 2 doses of mRNA-1273 primary series)

Summary by study part:

Separate shells will be provided for Part 1 and Part 2 of the study. All analyses and data summaries/displays will be provided by vaccination group.

Analysis Periods

The following analysis periods and treatment groups will be used for efficacy or immunogenicity analyses for Part 2, the blinded phase, unless specified otherwise:

Part 2 Group	**Description**	**Part 2 Blinded Phase Analysis Period for Efficacy or Immunogenicity**
mRNA-1273.214	Participants randomized to mRNA-1273.214 in the Blinded Phase	From randomization to earliest date of unblinding (inclusive), study

Placebo	Participants randomized to Placebo in the Blinded Phase	discontinuation, study completion, death, and data cutoff date

The following analysis period and treatment groups will be used for safety analysis for Part 2, the blinded phase, unless specified otherwise:

Part 2 Group	Description	Part 2 Blinded Phase Analysis Period for Safety
mRNA-1273.214	Participants received at least one dose of mRNA-1273.214 in the Blinded Phase	From the date of first injection to the earliest date of unblinding (inclusive), study discontinuation, study completion, death, and data cutoff date
Placebo	Participants only received Placebo in the Blinded Phase	

Subgroup Analysis

Safety, efficacy, and immunogenicity endpoints may be analyzed in select subgroups specified below as applicable:

- Sex (Female, Male)
- Baseline SARS-CoV-2 Status (Positive, Negative)
- Maternal COVID-19 vaccine status
- Maternal COVID-19 infection status
- Race
- Ethnicity

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by study part and vaccination group as defined in Section 6.1 and baseline SARS-CoV-2 status based on the Full Analysis Set for Part 1 and Randomization Set for Part 2:

- Randomization Set (Part 2)

- Full Analysis Set (Part 1 and Part 2)
- Per-Protocol (PP) Set (Part 1 and Part 2)
- Immunogenicity Subset (Part 1 and Part 2)
- Per-Protocol Immunogenicity Subset (PPIS) (Part 1 and Part 2)
- PPIS – Neg (Part 1 and Part 2)
- Safety Set (Part 1 and Part 2)
- Solicited Safety Set (Part 1 and Part 2)
- mITT Set (Part 1 and Part 2)
- mITT-1 Set (Part 1 and Part 2)

The percentage will be based on subjects in that vaccination group within the Full Analysis Set for Part 1 and in that vaccination group within the Randomization Set (as randomized) for Part 2, except the Solicited Safety Set and Safety Set for which the percentages will be based on the vaccination group in the Safety Set (as treated).

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by vaccination group based on Full Analysis Set for Part 1 and summarized by vaccination group based on the Randomization Set for Part 2:

- Received each dose of IP
- Prematurely discontinued before receiving the second dose of IP and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

A subject disposition listing will be provided, including informed consent, subjects who completed the study injection schedule, subjects who completed study, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

A subject who completed 12 months of follow up after the last injection received is considered to have completed the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (weeks), weight (kg, z-score), length (cm, z-score) and weight-for-height z-score. Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity, maternal COVID-19 infection history, maternal COVID-19 vaccine status, and maternal breastfeeding status. The summaries will be presented separately by vaccination group as defined in Section 6.1, based on the FAS, Randomization Set (Part 2), Per-Protocol (PP) Set, Per-Protocol Immunogenicity Subset (PPIS), PPIS-Neg, Safety Set, mITT Set, and mITT-1 Set.

Participants in Part 1 and Part 2 of the study who receive the same mRNA-1273.214 dose level may be combined. If the Safety Set differs from the Randomization Set in Part 2 (e.g., subjects randomized but not received any study injection; subjects received study vaccination other than the vaccination group they were randomized to), the analysis may also be conducted using the Randomization Set.

For screened failure subjects, age, as well as gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT

will be displayed in descending order of frequency of the total mRNA-1273.214 group with all dose level combined in Part 1 and the mRNA-1273.214 group in Part 2 and then alphabetically within SOC.

Medical history data and maternal medical history will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Table 4.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination groups as defined in Section 6.1 as follows:

- Any concomitant medications and non-study vaccination within 7 Days Post Injection
- Any concomitant medications and non-study vaccination within 28 Days Post Injection
- Antipyretic or analgesic medication within 28 Days Post Injection

A summary table of non-study vaccination that continued or newly received at or after the first injection through 28 days after the last injection will be provided by PT in descending frequency in the mRNA-1273.214 Total group with both dose levels combined for Part 1 and the mRNA-1273.214 group for Part 2.

A summary table of concomitant medications that continued or newly received at or after the first injection through 28 days after the last injection will be provided by PT in descending frequency of mRNA-1273.214 Total group with both dose levels combined for Part 1 and the mRNA-1273.214 group for Part 2.

Prior, concomitant and post medications and non-study vaccination, and maternal prior/concomitant medications and vaccination will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study IP administration data will be presented in a listing.

Study duration will be summarized by the following: since randomization, since the first injection, and since the second injection.

- Study duration from first injection (days) = earliest date of (study discontinuation, study completion, death, and data cutoff date) – date of first injection +1.
- Study duration from second injection (days) = earliest date of (study discontinuation, study completion, death, and data cutoff date) – date of second injection +1.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be identified, reviewed and finalized before database lock in accordance with the protocol deviation rule document.

The number and percentage of the subjects with each major protocol deviation type will be by vaccination group as defined in Section 6.1 based on the Full Analysis Set for Part 1 and will be provided by vaccination group based on the Randomization Set for Part 2.

Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing will be provided for COVID-19 impact.

6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to withdrawal from study vaccine and/or study participation, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA. A modified version of The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study for solicited ARs as presented in Table 7 in Section 8.11.3 of the protocol.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by study part and vaccination group unless otherwise specified.

Subgroup analysis may be done for the following subgroups:

- Sex (male, female)
- SARS-CoV-2 status at baseline
- Maternal COVID-19 vaccine status
- Maternal COVID-19 infection status
- Race
- Ethnicity

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not before exposure to study vaccine or any event already present that worsens after exposure to study vaccine. [Note: worsening of a pre-existing condition after vaccination will be reported as a new AE.]

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by vaccination group, and stage (up to 28 days after any vaccination for Part 1 and Part 2 separately and overall stage (throughout the study); see Section 6.1 for definitions of vaccination group and stage).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for AEs with counts of subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of total mRNA-1273.214 group with all dose level combined in Part 1 and mRNA-1273.214 group in Part 2 and then alphabetically within SOC. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity (the strongest relationship) in the summaries by severity, if subjects reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of subjects in the Safety Set within each vaccination group for Part 1 and Part 2 separately.

6.3.1.1.Incidence of Adverse Events

An overall summary of unsolicited AEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited AEs
- Any serious unsolicited AEs
- Any fatal unsolicited AEs
- Any unsolicited medically-attended AEs
- Any unsolicited AEs leading to discontinuation from study vaccine
- Any unsolicited AEs leading to discontinuation from participation in the study
- Any unsolicited Severe AEs
- Any unsolicited Non-serious AEs
- Any unsolicited Non-serious and Severe AEs
- Any AESI of multisystem inflammatory syndrome in children (MIS-C)
- Any AESI of myocarditis and/or pericarditis
- Any AESI other than MIS-C and myocarditis and/or pericarditis

The table will also include number and percentage of subjects with unsolicited AEs that are treatment-related in each of the above categories.

In addition, separate listings containing individual subject adverse event data for unsolicited AEs, unsolicited AEs leading to discontinuation from study vaccine, unsolicited AEs leading to discontinuation from participation in the study, severe AEs, serious AEs, unsolicited medically-attended AEs, AESI other than MIS-C and myocarditis and/or pericarditis, AESI of MIS-C and AESI of myocarditis and/or pericarditis will be provided separately.

6.3.1.2.AEs by System Organ Class and Preferred Term

The following summary tables of AEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All unsolicited AEs
- All unsolicited AEs that are treatment-related
- All serious unsolicited AEs
- All serious unsolicited AEs that are treatment-related
- All unsolicited AEs leading to discontinuation from study vaccine
- All unsolicited AEs leading to discontinuation from participation in the study
- All unsolicited AEs leading to discontinuation from participation in the study that are treatment-related
- All unsolicited Severe AEs
- All unsolicited Severe AEs that are treatment-related
- All unsolicited medically-attended AEs
- All unsolicited medically-attended AEs that are treatment-related
- All AESI of MIS-C
- All AESI of myocarditis and/or pericarditis
- All AESI other than MIS-C and myocarditis and/or pericarditis
- All unsolicited AEs with occurrence in ≥1% of participants in any treatment group based on PT

Additionally, the following summary tables of AEs will be provided by PT using frequency counts and percentages:

- All unsolicited AEs
- All unsolicited AEs, presented by Standardized MedDRA Queries (SMQ) and PT.

6.3.1.3.AEs by System Organ Class, Preferred Term and Severity

The following summary table of AEs will be provided by SOC, PT, and maximum severity (mild < moderate < severe) using frequency counts and percentages:

- All unsolicited AEs (Any vs. Related)

6.3.2. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs).

The following local ARs will be solicited by the eDiary: pain/tenderness at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and groin or underarm swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: fever, irritability/crying, sleepiness, and loss of appetite.

The AR categories are presented in Table 7 in the protocol.

The solicited ARs will be graded based on the grading scales presented in Table 7 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). Investigator will assess Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post injection, the participant's parent(s)/ LAR(s) should notify the site to provide an end date to close out the event on the reactogenicity page of the eCRF.

All solicited ARs (local and systemic) will be considered causally related to injection.

Analyses of solicited ARs will be provided by study part and treatment group for each injection (first or second) based on the associated subset of Solicited Safety Set, i.e. First (Second) Injection Solicited Safety Set, unless otherwise specified.

The number and percentage of subjects who reported each individual solicited local AR (has a toxicity grade of Grade 1 or greater) and solicited systemic AR (has a toxicity grade of Grade 1 or greater) during the 7-day follow-up period after each injection will be tabulated by vaccination group, toxicity grade, and injection (i.e., first or second injection). The number and percentage of subjects who reported each individual solicited AR will also

be summarized by vaccination group, toxicity grade, days of reporting and injection. In addition, a bar plot will be created to display the percentage of participants who reported each individual solicited AR after each injection.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The onset of individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by vaccination group, study day relative to the corresponding injection (Day 1 through Day 7), and injection.

The duration will be calculated as the end date/day of the solicited AR event – start date/day of the solicited AR event + 1, regardless of whether it is intermittent or continued. If the solicited AR continues beyond 7 days, the days a solicited AR is reported after 7 days will be included (e.g., an event that lasted 5 days in the first 7 days post injection and 3 days beyond 7 days post injection, the duration will be reported as 8 [5+3] days).

Characteristics of solicited ARs during the 7-day follow-up period after each injection will be provided, including descriptive statistics of day of onset and duration in days, as well as number and percentage of solicited ARs persisting beyond 7 days.

Solicited ARs collected on eDiary and those collected on reactogenicity aCRF will be provided in a listing, and the maximum grade from eDiary and aCRF will be presented. All solicited ARs that continue beyond 7 days post injection will be presented in separate data listings.

6.3.3. Physical Examinations and Vital Signs

Vital signs, including length/height, weight, and body temperature (via axillary route) will be presented in a listing.

Abnormal physical examination findings will be reported on the medical history or adverse events eCRF, as appropriate.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PPIS-Neg as the primary analysis population for both parts, unless otherwise specified. Participants from Part 1 and Part 2 in

the PPIS-Neg population who receive the same mRNA-1273.214 dose level selected for Part 2 may be combined for immunogenicity analyses.

The geometric mean concentration (GMC) and GM level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity concentrations or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity concentrations or levels within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity concentrations or levels for subject i at time points j and k, $j \neq k$,where k represent pre-injection baseline at Day 1.

6.4.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Assessments (SoAs) in Appendix E.

Immunogenicity assessments for both Part 1 and Part 2:

- Serum nAb concentration against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays, including VOC Omicron.
- Serum bAb level as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 S protein.
- Serum bAb level as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

6.4.2. Hypothesis Testing Strategy for Immunogenicity

The hypothesis tests for noninferiority, superiority, and "super" superiority of mRNA-1273.214 against Omicron as compared to mRNA-1273 primary series against Omicron will be performed sequentially. The noninferiority hypotheses (hypotheses HA^1 and HA^2) will be tested first.

Once noninferiority is demonstrated based on both GMC or GM level and SRR, superiority (hypotheses HA^3 and HA^4) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1, superiority based on GMC or GM level is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 0%, superiority based on seroresponse is demonstrated.

Once superiority is demonstrated based on both GMC or GM level and SRR, "super" superiority (hypotheses HA^5 and HA^6) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1.5, "super" superiority based on GMC or GM level is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 10%, "super" superiority based on seroresponse is demonstrated.

6.4.3. Primary Analysis of Antibody-Mediated Immunogenicity Endpoints

For Part 2, the immune response as measured by the serum Ab GM value and SRR against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 will be compared to that of the young adult participants (18-25 years) at 28 days after the second dose of mRNA-1273 primary series in Study mRNA-1273-P301.

An analysis of covariance (ANCOVA) model will be carried out with the serum Ab value at 28 days after the second dose of IP (Day 85 for Study P206, Day 57 for Study P301) as the dependent variable and a group variable (mRNA-1273.214 vs. mRNA-1273) as the fixed variable, adjusted by the baseline serum Ab value. The serum Ab GM value at Day 85 for Study P206 and serum Ab GM value at Day 57 for Study P301 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (Study P206 vs. Study P301) will be estimated by the ratio of GLSM. Its 2-sided 95% CI will also be provided to assess the difference in immune response between the Study P206 and Study P301 at 28 days after the second dose of IP.

The noninferiority of the GM value of mRNA-1273.214 compared with mRNA-1273 primary series will be demonstrated if the lower bound of the 95% CI of the GMR > 0.667.

In addition, the serum Ab GM value with its 95% CI and GMR with 95% CI will be provided at 28 days after the second dose of IP. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale. Descriptive summary statistics for serum Ab values including median, minimum, and maximum will also be provided.

The GMFR of serum Ab values with its 95% CI at 28 days after the second dose of IP over baseline (pre-Dose 1 of primary series) will be provided. Its 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

The number and percentage of participants with seroresponse due to vaccination will be provided with 2-sided 95% CI using Clopper-Pearson method at 28 days after the second dose of IP, where seroresponse at subject level is defined two ways:

1. as an Ab value change from baseline (pre-Dose 1 of primary series) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.
2. as an Ab value change from baseline (pre-Dose 1 of primary series) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline is ≥ 4 × LLOQ.

The SRR difference with its 95% CI (using Miettinen-Nurminen score method) between pediatric participants receiving mRNA-1273.214 in Study P206 at Day 85 and adult participants receiving mRNA-1273 primary series in Study P301 at Day 57 will be provided.

The noninferiority of the SRR of mRNA-1273.214 compared with that of mRNA-1273 primary series will be demonstrated if the lower bound of the 95% CI of the SRR difference is > -5%.

The table below lists possible scenarios of GMR and SRR difference results and corresponding immunogenicity hypothesis testing conclusions.

Endpoints	Scenario		Conclusion
GMC or GM level Ratio	1	Lower bound of 95% CI of GMR (GMC_{P206}/ GMC_{P301} or GM $level_{P206}$/ GM $level_{P301}$) ≤ 0.667	Non-inferiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg primary series (PS) in P301 based on GMR is not demonstrated

	2	0.667 < Lower bound of 95% CI of GMR (GMC_{P206}/ GMC_{P301} or GM $level_{P206}$/ GM $level_{P301}$) ≤ 1	Non-inferior of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on GMR is demonstrated but superiority is not demonstrated.
	3	1< Lower bound of 95% CI of GMR (GMC_{P206}/ GMC_{P301} or GM $level_{P206}$/ GM $level_{P301}$) ≤ 1.5	Superiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on GMR is demonstrated but "super" superiority is not demonstrated
	4	Lower bound of 95% CI of GMR (GMC_{P206}/ GMC_{P301} or GM $level_{P206}$/ GM $level_{P301}$) > 1.5	"Super" superiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301based on GMR is demonstrated
SRR Difference	1	Lower bound of 95% CI of SRR difference (SRR_{P206} - SRR_{P301}) ≤ -5 %	Non-inferiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on SRR difference is not demonstrated
	2	-5% < Lower bound of 95% CI of SRR difference (SRR_{P206} - SRR_{P301}) ≤ 0	Non-inferiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on SRR difference is demonstrated but superiority is not demonstrated
	3	0 < Lower bound of 95% CI of SRR difference (SRR_{P206} - SRR_{P301}) ≤ 10%	Superiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on SRR difference is demonstrated but "super" superiority is not demonstrated
	4	Lower bound of 95% CI of SRR difference (SRR_{P206} - SRR_{P301}) > 10%	"Super" superiority of mRNA-1273.214 in P206 as compared to mRNA-1273 100 µg PS in P301 based on SRR difference is demonstrated

6.4.4. Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints

The following secondary immunogenicity evaluations will be performed.

- For each group in Part 1, GM level of SARS-CoV-2-specific serum Ab with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point at which blood samples are collected for immunogenicity: the number of subjects (n), median, minimum and maximum.

- For Part 2, the immune response as measured by the serum Ab GM value and SRR against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose will be compared to the serum Ab GM value and SRR at Day 57 (at 28 days after the second dose) against original strain after mRNA-1273 primary series in Study P301 using the same analysis methods described in Section 6.4.3.

- For Part 2, the immune response as measured by the serum Ab GM value and SRR against SARS-CoV-2 original strain at 28 days after the second dose will be compared to the serum Ab GM value and SRR at Day 57 (at 28 days after the second dose) against original strain after mRNA-1273 primary series in Study P301 using the same analysis methods described in Section 6.4.3.

6.4.5. Exploratory Analysis of Antibody-Mediated Immunogenicity Endpoints

The below exploratory analyses of immunogenicity for Part 1 and/or Part 2 may be performed if applicable.

- GM level of SARS-CoV-2-specific bAb with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

- GM fold-rise (GMFR) of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each postbaseline timepoint over pre-injection baseline at Day 1. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

Proportion of subjects with fold-rise ≥ 2, and fold-rise ≥ 4 of serum SARS-CoV-2 specific bAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs.

- GMC of SARS-CoV-2-specific nAb concentrations with corresponding 95% CI will be provided at each time point using the same method mentioned above.
- GMFR of SARS-CoV-2-specific nAb concentrations with corresponding 95% CI will be provided at each postbaseline timepoint over pre-injection baseline at Day 1 using the same method mentioned above.

  Proportion of subjects with fold-rise ≥ 2, and fold-rise ≥ 4 of serum nAb from Visit Day 1 (baseline) at each post-injection time points will be tabulated with 2-sided 95% Clopper-Pearson CIs.

- Proportion of subjects with seroresponse due to vaccination will be tabulated with 2-sided 95% Clopper-Pearson CIs at each postbaseline timepoint. The definition of seroresponse can be found in Section 6.4.2.
- A plot to display the Ab value change from baseline to 28 days after the last dose in each vaccination group against the maternal factors (maternal COVID-19 vaccine status and maternal COVID-19 infection status) stratified by infant baseline SARS-CoV-2 status will be provided.

6.5. Efficacy Analysis

The exploratory analyses of the effectiveness in Part 2 will be performed primarily on the PP Set, unless specified otherwise. Analysis of effectiveness will be performed to evaluate the incidence rates of the following efficacy endpoints:

- COVID-19
- SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity
- Asymptomatic SARS-CoV-2 Infection

Subjects will be included in the treatment group to which they were randomized in Part 2.

Baseline SARS-CoV-2 status is described in Section 6.1. Baseline SARS-CoV-2 status, the serology test results at baseline, the RT-PCR test results at baseline will be summarized by treatment group.

Participants with baseline positive or missing SARS-CoV-2 status will be excluded from the PP Set.

In this study, the serology test results and the RT-PCR test results will be summarized by visit.

6.5.1. Endpoint Definition/Derivation

6.5.1.1. CDC Case Definition of COVID-19

The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on CDC case definition, starting 14 days after each injection of mRNA-1273.214, will be summarized using incidence rate (number of cases divided by the total person-time).

Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results.

A positive PCR result of the eligible symptoms are summarized below in Table 1.

Table 1 Derivation for CDC Case Definition of COVID-19

	COVID-19
Postbaseline PCR results	Positive, **AND**
Systemic Symptoms	at least **ONE** of the following systemic symptoms: Fever (temperature ≥ 38° C/≥ 100.4° F) or chills (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding; OR
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours).

The date of documented CDC Case Definition of COVID-19 (case) will be the later date of ([systemic symptom reported, or respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented CDC Case Definition of COVID-19 will be the

later date of the following two dates (date of positive PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

- Date of positive PCR test,
- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported
    - Systemic symptoms: earliest date of the eligible systemic symptom is reported

The time to the first occurrence of CDC Case Definition of COVID-19 will be calculated as:

Time to the first occurrence of CDC Case Definition of COVID-19 = Date of documented CDC Case Definition of COVID-19 – Date of Randomization + 1.

COVID-19 will be assessed primarily for cases starting 14 days after second injection, i.e. date of documented COVID-19 – Date of the 2nd injection ≥ 14. COVID-19 may also be assessed for cases starting after first injection, 14 days after first injection, and starting after second injection.

6.5.1.2.SARS-CoV-2 Infection or COVID-19 regardless of symptomatology or severity

The incidence of SARS-CoV-2 infection starting 14 days after each injection of mRNA-1273.214 will be summarized using incidence rate (number of cases divided by the total person-time).

SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:

- Ab level against SARS-CoV-2 nucleocapsid protein that is negative at Day 1, but becomes positive (as measured by ligand-binding assay) postbaseline, OR
- Positive RT-PCR postbaseline.

Derivation of SARS-CoV-2 Infection is summarized in Table 2 below.

Table 2 Derivation for SARS-CoV-2 Infection

	Postbaseline assessments	

Baseline SARS-CoV-2 Status	PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	**Endpoint**: SARS-CoV-2 infection
Negative at Baseline	**Positive** (either at nasal swab test, or at symptom-prompt nasal swab test)		Case
Negative at Baseline		**Positive** (at Post baseline visit or later) as measured by *ligand-binding assay*	Case

The incidence rate will be calculated as the number of cases divided by the total person-time.

The date of documented infection will be the earlier of:

- Date of positive postbaseline RT-PCR result, or
- Date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid

Time to the First SARS-CoV-2 infection = Date of the First documented infection – Date of randomization + 1.

SARS-CoV-2 infection regardless of symptomatology and severity will be assessed primarily for cases starting 14 days after second injection. SARS-CoV-2 infection may also be assessed for cases starting after first injection, 14 days after first injection, and starting after second injection.

6.5.1.3.Asymptomatic SARS-CoV-2 Infection

The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or serology tests obtained postbaseline visits counted starting 14 days after the second injection in Part 2 participants with negative SARS-COV-2 status at baseline will be summarized by incidence rate (number of cases divided by the total person-time).

Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically:

- Absence of COVID-19 symptoms +/- 14 days from at least one positive test below:

- bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by ligand-binding assay) postbaseline, OR
- Positive RT-PCR test postbaseline (at scheduled or unscheduled/illness visits)

The date of documented asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid due to infection, or positive RT-PCR at scheduled visits, with absence of symptoms.

The time to the asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection test – Date of randomization + 1.

Asymptomatic SARS-CoV-2 infection will be assessed primarily for cases starting 14 days after second injection. COVID-19 may also be assessed for cases starting after first injection, 14 days after first injection, and starting after second injection.

6.5.2. Analysis Method

The number and percentage of subjects who had an event (i.e., COVID-19 case) will be summarized for the PP set, and FAS.

The incidence rate will be calculated as the number of cases divided by the total person-time (person-year or person-month). The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Person-time is defined as the total time from randomization date in Part 2 to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earlier.

Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with COVID-19 or SARS-CoV-2 infection during the study will also be provided.

6.5.3. Sensitivity and Subgroup Analysis

Sensitivity analysis for key efficacy endpoints will be performed with the same methods described above based on the mITT Set and mITT-1 Set, with cases counted starting from randomization in Part 2. A sensitivity analysis will be performed based on a modified version of the endpoint definition, including COVID-19 non-RT-PCR tests.

Subgroup analysis may be done for the following subgroups:

- Sex (male, female)
- SARS-CoV-2 status at baseline
- Maternal COVID-19 vaccine status
- Maternal COVID-19 infection status
- Breastfeeding history
- Race
- Ethnicity

6.6. Interim Analyses

Part 1: Interim analyses of safety and immunogenicity will be performed after all treated participants in one or both arms have completed 28 days after the last dose of mRNA-1273.214. Note that two interim analyses will be performed. The Arm 2 interim analysis may include data from Arm 1.

Part 2: An interim analysis of safety and immunogenicity will be performed after all participants have completed 28 days after the last dose of mRNA-1273.214. This interim analysis will be considered the primary analysis for immunogenicity.

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an end of study clinical study report (CSR), including individual listings.

6.7. Data Safety Monitoring Board

Safety oversight will be under the direction of a DSMB composed of external, independent consultants with relevant expertise. Members of the DSMB will be independent from study conduct and free of conflict of interest. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter. Statistical analysis outputs for the DSMB review will also be specified in the charter.

7. Changes from Planned Analyses in Protocol

On 18Sep2023, the study initiated an enrollment pause in direct response to emergency use authorization of an updated COVID-19 vaccine in children 6 months of age and older in the United States. Prior to the enrollment pause, 18 participants were enrolled in Part 1 Arm 2. As a result, the Part 1 Arm 2 interim analysis will be conducted after 18 participants have completed 28 days after last dose of mRNA-1273.214 rather than after the total planned enrollment in this arm (50 participants). This change does not impact the primary and/or key secondary objectives/hypotheses or the related statistical methods.

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September2007[cited2019 Apr 10][10 screens]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

9. List of Appendices

9.1. Appendix A: Standards for Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

9.2. Appendix B: Analysis Visit Windows for Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 3 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 3 Visit Window

Visit	Target Study Day	Visit Window in Study Day
Nasal Swabs for SARS-CoV-2		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 57 (Month 2)	57 (Date of Second Injection)	[2, 71]
Day 85 (Month 3)	85	[72,161]
Day 237 (Month 8)	237	[162, 330]
Day 422 (Month 14)	422	≥331
SARS-CoV-2 Serology		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 85 (Month 3)	85	≥2
Immunogenicity		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 85 (Month 3)	85	[2,161]
Day 237 (Month 8)	237	[162, 330]
Day 422 (Month 14)	422	≥331

9.3. Appendix C: Imputation Rules for Missing Prior/Concomitant Medications, Non-Study Vaccinations, and Maternal Prior/Concomitant Medications

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    - If only Day is missing, use the first day of the month, unless:
        - The medication end date is after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection
    - If Day and Month are both missing, use the first day of the year, unless:
        - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection
    - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
    - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
    - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
    - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 4 below.

Table 4 Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations

	Medication Stop Date		
Medication Start Date	**< First Injection Date of IP**	**≥ First Injection Date and ≤ 28 Days After Last Injection**	**> 28 Days After Last Injection [2]**
< First injection date of IP [1]	P	P, C	P, C, A
≥ First injection date and ≤ 28 days after last injection	-	C	C, A
> 28 days after last injection [3]	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date
[3] on the day of last injection and the 27 subsequent days

9.4. Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:
    - If only Day is missing, use the first day of the month, unless:
        - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.
    - If Day and Month are both missing, use the first day of the year, unless:
        - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection
    - If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.
2. Missing or partial AE end dates will not be imputed.

9.5. Appendix E: Schedule of Assessments (Parts 1 and 2)

Visit Number	**0**	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**--**		**8**	**--**		**9**	**USV**
Type of Visit	**C**	**C**	**C**	**TM**	**SFU**	**C**	**C**	**TM**	**C**	**SFU**		**C**	**SFU**		**C**	**C**
Month Time Point		**M0**	**M0**		**SC**	**M2**	**M2**		**M3**	**eDiary**	**SC**	**M8**	**eDiary**	**SC**	**M14**	**Up to M14**
Study Visit Day	**D-28 to D-1 (Screening)[1]**	**D1 (Baseline)**	**D4[2]**	**D8**	**D29[3]**	**D57[4]**	**D60[2]**	**D64[4]**	**D85[4, 5]**	**Every 4 weeks D99–D211[3, 4]**	**Every 4 weeks D113–D225[3, 4]**	**D237[3]**	**Every 8 weeks D265–D377[4, 6]**	**Every 8 weeks D293–D405[3, 4]**	**D422 365 days after D57[3, 4]**	**Unscheduled Visit[7, 8]**
Window Allowance (Days)	**-**	**-**	**± 1**	**+ 3**	**+3**	**-14/+ 7**	**± 1**	**+ 3**	**-14/+ 7**	**± 7**	**± 7**	**± 14**	**± 7**	**± 7**	**± 14**	**N/A**
Days Since Most Recent Injection	**-**	**0**	**3**	**7**	**28**	**56**	**3**	**7**	**28**	**-**	**-**	**180**	**-**	**-**	**365**	
ICF, demographics, concomitant medications, medical history[9]	X															
Review of inclusion and exclusion criteria	X	X														
Physical examination and vital signs including length/height, weight and body temperature[10]	X	X	X			X	X		X			X			X	X
Randomization		X														
Study injection[11]		X				X										
Blood sample for vaccine immunogenicity[12]		X							X			X			X	

Visit Number	**0**	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**--**		**8**	**--**		**9**	**USV**
Type of Visit	**C**	**C**	**C**	**TM**	**SFU**	**C**	**C**	**TM**	**C**	**SFU**		**C**	**SFU**		**C**	**C**
Month Time Point		**M0**	**M0**		**SC**	**M2**	**M2**		**M3**	**eDiary**	**SC**	**M8**	**eDiary**	**SC**	**M14**	**Up to M14**
Study Visit Day	**D-28 to D-1 (Screening)[1]**	**D1 (Baseline)**	**D4[2]**	**D8**	**D29[3]**	**D57[4]**	**D60[2]**	**D64[4]**	**D85[4, 5]**	**Every 4 weeks D99–D211[3, 4]**	**Every 4 weeks D113–D225[3, 4]**	**D237[,3]**	**Every 8 weeks D265–D377[4, 6]**	**Every 8 weeks D293–D405[3, 4]**	**D422 365 days after D57[3, 4]**	**Unscheduled Visit[7, 8]**
Window Allowance (Days)	**-**	**-**	**± 1**	**+ 3**	**+3**	**-14/+ 7**	**± 1**	**+ 3**	**-14/+ 7**	**± 7**	**± 7**	**± 14**	**± 7**	**± 7**	**± 14**	**N/A**
Days Since Most Recent Injection	**-**	**0**	**3**	**7**	**28**	**56**	**3**	**7**	**28**	**-**	**-**	**180**	**-**	**-**	**365**	
Blood sample for SARS-CoV-2 surveillance[13]		X							X							
Nasal swab sample for SARS-CoV-2[13]		X				X			X			X			X	X
Surveillance for COVID-19/illness visit[7]				X	X	X		X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[8]		X				X										
Review of eDiary data			X	X			X	X								
Follow-up safety telephone calls[14]					X						X			X		
Recording of unsolicited AEs		X	X	X	X	X	X	X	X							

Visit Number	0	1	2	3		4	5	6	7	--		8	--		9	USV
Type of Visit	C	C	C	TM	SFU	C	C	TM	C	SFU		C	SFU		C	C
Month Time Point		M0	M0		SC	M2	M2		M3	eDiary	SC	M8	eDiary	SC	M14	Up to M14
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D4[2]	D8	D29[3]	D57[4]	D60[2]	D64[4]	D85[4, 5]	Every 4 weeks D99–D211[3, 4]	Every 4 weeks D113–D225[3, 4]	D237[3,3]	Every 8 weeks D265–D377[4, 6]	Every 8 weeks D293–D405[3, 4]	D422 365 days after D57[3, 4]	Unscheduled Visit[7, 8]
Window Allowance (Days)	-	-	± 1	+ 3	+3	-14/+ 7	± 1	+ 3	-14/+ 7	± 7	± 7	± 14	± 7	± 7	± 14	N/A
Days Since Most Recent Injection	-	0	3	7	28	56	3	7	28	-	-	180	-	-	365	
Recording of MAAEs, SAEs, and AESIs and concomitant medications and procedures relevant to or for the treatment of the MAAE and SAE[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and procedures and nonstudy vaccinations[16]		X	X	X	X	X	X	X	X		X	X		X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report form; EDC = electronic data capture; eDiary = electronic diary; FDA = Food and Drug Administration; ICF = informed consent form; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; N/A = not applicable; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SFU = safety follow-up; TM = telemedicine visit or call; USV= unscheduled visit.Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency (FDA March 2020), investigators may convert study site visits to home visits or telemedicine visits (with the exception of Screening, Day 1, Day 57, Day 85, Day 237, and Day 422) with the approval of the Sponsor (home visits also require site IRB approval).

1. Screening Visit and Day 1 may be combined on the same day. Additionally, the Screening Visit may be performed over multiple visits if performed within the 28-day screening window.

2. Day 4 and Day 60 clinic visits will only be performed in Part 1 of study.
3. Safety follow-up via a safety telephone call will be performed on Day 29, every 4 weeks from Day 113 to Day 225, and every 8 weeks from Day 293 to Day 405.
4. If the visit for the second dose (Day 57) is disrupted and cannot be completed at Day 57 (–14/+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the visit window may be extended to Day 57 + 14 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the intervisit interval from the actual date of the second dose.
5. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a remote evaluation via a telemedicine visit or call should be conducted in place of the study site visit (except for dosing visits and visits that require a blood draw). The remote evaluation should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits, with the exception of screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant's parent(s)/LAR(s) via informed consent and have prior approval from the Sponsor (or its designee).
6. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 99 to Day 211 and every 8 weeks from Day 265 to Day 377.
7. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the pre-specified criteria of suspicion for COVID-19, the participant will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit to include a nasal swab sample (for RT-PCR testing to evaluate for the presence of SARS-CoV-2 infection) and other clinical evaluations. If a study site visit is not possible, a home visit may be arranged to collect the nasal swab sample and conduct clinical evaluations. The study site may collect an additional nasal swab sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
8. At each injection visit, participants' parent(s)/LAR(s) will record data into the eDiary starting approximately 30 minutes after injection under the supervision of the study site staff to ensure successful entry of assessment. Participants' parent(s)/LAR(s) will continue to record entries in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection. Capturing details of ARs in the eDiary should not exceed 7 days after each vaccination. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the event should be reviewed by the study site staff either via a telephone call or at an unscheduled study site visit.
9. Verbal medical history is acceptable.
10. A full physical examination and vital signs assessments, including length/height, weight, and body temperature, will be performed at the Screening Visit (and on Day 1, if Day 1 and Screening Visit occur on separate days). Symptom-directed physical examinations and vital signs assessments will be performed on Day 1, Day 4 (in Part 1), Day 57, Day 60 (in Part 1), Day 85, Day 237, Day 422, and USV, and may be performed at other time points at the discretion of the investigator. Body temperature should be measured on each injection day prior to injection. Body temperature must be measured via the axillary route and any axillary reading of ≥ 37.8° C/≥ 100° F may be confirmed by a rectal measurement. On each injection day before injection and again 7 days after injection, the injection site should be examined. Any clinically significant finding identified during a study visit should be reported as an MAAE. Participants who are febrile (≥ 38.0° C/≥ 100.4° F) before injection on Day 1 or Day 57 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.
11. Study injection postdose observation will be 60 minutes for Part 1 and 30 minutes for Part 2.
12. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (baseline) blood sample cannot be obtained, the participant could be rescheduled within the allowable screening period one time. If a blood sample still cannot be obtained at the rescheduled visit, then the participant will be considered a screen failure due to inability to satisfy inclusion criterion 3.
13. The nasal swab and blood sample (collected before dosing on each injection day and on other scheduled days per the SoA) will be used to ascertain the presence or history of SARS-CoV-2 infection via RT-PCR and serum binding antibody specific to SARS-CoV-2 nucleocapsid, respectively.
14. Medically qualified and trained study site personnel will call all participants to collect information relating to any MAAEs, SAEs, AEs leading to study withdrawal and information on concomitant medications associated with those events and any nonstudy vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on any COVID-19 symptoms the participant may experience.

15. A list of AESIs pertinent to this study is maintained by the Sponsor and provided to each investigator. All SAEs and AESIs will be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE or AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line.
16. All concomitant medications and procedures will be recorded through 28 days after each injection (through the completion of the Day 85 visit). All nonstudy vaccines given at any time during the study period should be recorded. All concomitant medications relevant to or for the treatment of an SAE, MAAE, or AESI will be recorded from Day 1 through the final visit (Day 422).