16.1.9 Documentation of Statistical Methods

This section contains the following document:

Statistical analysis plan version 4.0, dated 03 Jun 2021

ModernaTX, Inc.

Protocol mRNA-1273-P201

A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Statistical Analysis Plan

SAP Version 4.0
Version Date of SAP: 03 June 2021

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AR	adverse reaction
BMI	body mass index
bAb	binding antibody
CI	confidence interval
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	full analysis set
GCP	Good Clinical Practice
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
IgG	immunoglobulin G
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MSD	Meso scale discoversy
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
OL	open-label
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
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-P201, is based on the most recent approved clinical study protocol (CSP), Version Amendment 6, dated 28-APR-2021. The most recent approved electronic case report form (eCRF) Version 5.005, dated 24-FEB-2021.

This SAP version 4.0 is to update the planned analyses according to the study protocol, Amendment 6, which is designed to transition to Part B, the Open-Label Interventional Phase following authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA) and to add an analysis at the end of Part A.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 4) 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-P201 is a Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of messenger ribonucleic acid (mRNA)-1273 SARS-CoV-2 vaccine in adults who aged 18 years and older.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

2. Study Objectives

2.1. Primary Objective (Part A, Blinded)

2.1.1. Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart.

2.1.2. Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific binding antibody (bAb).

2.2. Secondary Objectives (Part A, Blinded)

The secondary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

2.3. Exploratory Objectives (Part A, Blinded)

The exploratory objectives are the following:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum.
- To describe the ratio or profile of specific bAb relative to nAb in serum.
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29).
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2.
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.

2.4. Primary Objective (Part B, Open Label)

2.4.1. Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 vaccine administered as 2 doses 28 days apart.

2.4.2. Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 vaccine administered as 2 doses 28 days apart, as assessed by the level of specific bAb.

2.5. Secondary Objectives (Part B, Open Label)

The secondary objective is to evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 vaccine administered as 2 doses 28 days apart, as assessed by the titer of nAb.

2.6. Exploratory Objectives (Part B, Open Label)

The exploratory objectives are the following:

- To profile S protein-specific serum Ig class and subclass and nAb in serum.
- To describe the ratio or profile of specific bAb relative to nAb in serum.
- To describe initial immunogenicity responses at various time points following a booster dose, where applicable.
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2.
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.

3. Study Endpoints

3.1. Primary Endpoints (Part A, Blinded)

3.1.1. Primary Safety Endpoints

The primary safety objective 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) through the entire study period.
- Serious AEs (SAEs) throughout the entire study period.
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only).
- Vital sign measurements and physical examination findings.

3.1.2. Primary Immunogenicity Endpoints

Level of SARS-CoV-2-specific bAb measured by enzyme-linked immunosorbent assay (ELISA) on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13), as applicable.

3.2. Secondary Endpoints (Part A, Blinded)

The secondary objective will be evaluated by the following endpoints:

- Titer of SARS-CoV-2-specific nAb on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13), as applicable.
- Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the lower limit of quantification (LLOQ) to equal to or above LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers, as applicable.

3.3. Exploratory Endpoints (Part A, Blinded)

The exploratory endpoints are the following:

- Serum titers of S protein-specific binding Ig by class and subclass and nAb in serum.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum.
- Clinical severity and immune response of participants infected by SARS-CoV-2.
- Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect non-vaccine antigens of SARS-CoV-2.

3.4. Primary Endpoints (Part B, Open Label)

3.4.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.
- Unsolicited AEs through 28 days after each injection.

- MAAEs through the entire study period.
- SAEs throughout the entire study period.
- Vital sign measurements and physical examination findings.

3.4.2. Primary Immunogenicity Endpoints

- For participants receiving 100 µg of mRNA-1273 as 2 doses 28 days apart: Level of SARS-CoV-2-specific bAb measured by ELISA on OL-Day 1, OL-Day 8, OL-Day 15, OL-Day 29 (OL-M1), OL-Day 57 (OL-M2), and OL-Day 209 (OL-M7).
- For participants receiving 50 µg of mRNA-1273 as a single booster: Level of SARS-CoV-2-specific bAb measured by ELISA on OL-Day 1, OL-Day 8, OL-Day 15, OL-Day 29 (OL-M1), OL-Day 57 (OL-M2), and OL-Day 181 (OL-M6).

3.5. Secondary Endpoints (Part B, Open Label)

The secondary objective will be evaluated by the following endpoints:

- For participants receiving 100 µg of mRNA-1273 as 2 doses 28 days apart: Titer of SARS-CoV-2-specific nAb on Open Label (OL)- Day 1, OL-Day 8, OL- Day 15, OL- Day 29 (OL-M1), OL- Day 57 (OL-M2), and OL- Day 209 (OL-M7).
- For participants receiving 50 µg of mRNA-1273 as a single booster: Titer of SARS-CoV-2-specific nAb on OL-Day 1, OL-Day 8, OL-Day 15, OL-Day 29 (OL-M1), OL-Day 57 (OL-M2), and OL-Day 181 (OL-M6).
- For participants receiving 100 µg of mRNA-1273 as 2 doses 28 days apart: Seroconversion on OL-Day 8, OL-Day 15, OL-Day 29 (OL-M1), OL-Day 57 (OL-M2), and OL-Day 209 (OL-M7).
- For participants receiving 50 µg of mRNA-1273 as a single booster: Seroconversion on OL-Day 8, OL-Day 15, OL-Day 29 (OL-M1), OL-Day 57 (OL-M2), and OL-Day 181 (OL-M6), and the proportion of participants with a ≥2-, ≥3-, or ≥4-fold rise in antibody titer from open-label baseline.

3.6. Exploratory Endpoints (Part B, Open Label)

The exploratory endpoints are the following:

- Serum titers of S protein-specific binding Ig assessed by class and subclass and nAb in serum.

- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum.
- Clinical severity and immune response of participants infected by SARS-CoV-2.
- Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect non-vaccine antigens of SARS-CoV-2.

4. Study Design

4.1. Overall Study Design

This is a two-part, Phase 2a study: Part A and Part B. Participants in Part A, the Blinded Phase of the study, are blinded to their treatment assignment. Given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met in a separate Phase 3 efficacy study (COVE study) conducted by the Sponsor, this Phase 2a study will move to Part B, Open-Label Interventional Phase.

Part B, the Open-label Interventional Phase of this study is designed to offer participants who received placebo in Part A of this study an option to receive 2 injections of open-label mRNA-1273. Participants who received 1 or 2 injections of mRNA-1273 (50 µg or 100 µg) in Part A of this study will proceed to Part B, open-label, and will be offered a single booster dose of mRNA-1273 (50 µg).

4.1.1. Part A, the Blinded Phase

The Blinded Phase of this study is an observer-blind, randomized, and placebo-controlled, with adult participants at least 18 years of age. The study schematic is presented in Figure 1.

Two dose levels (50 µg and 100 µg), will be evaluated in this study, based in part on initial safety data from the Phase 1 study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo.

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment (Figure 2). Before initiating study treatment of the remaining

participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC).

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

Figure 1 Study Design Schematic

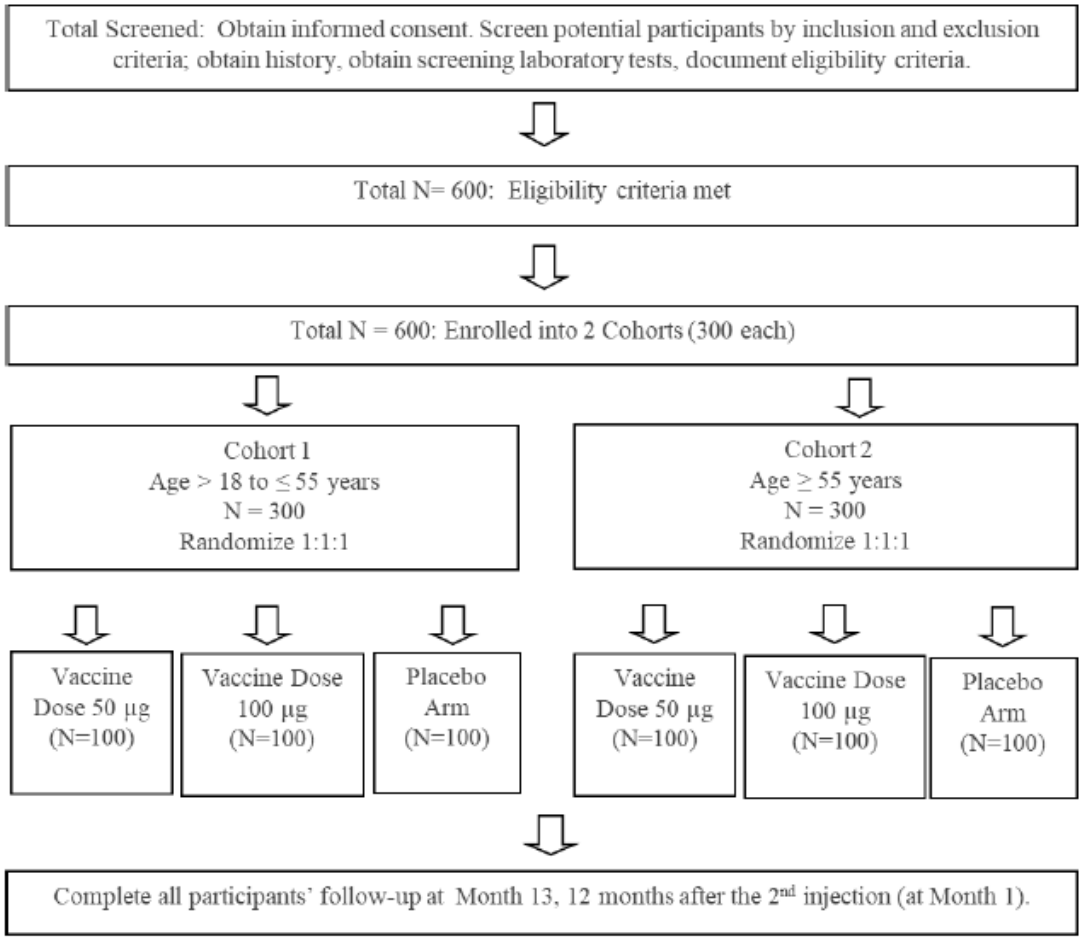
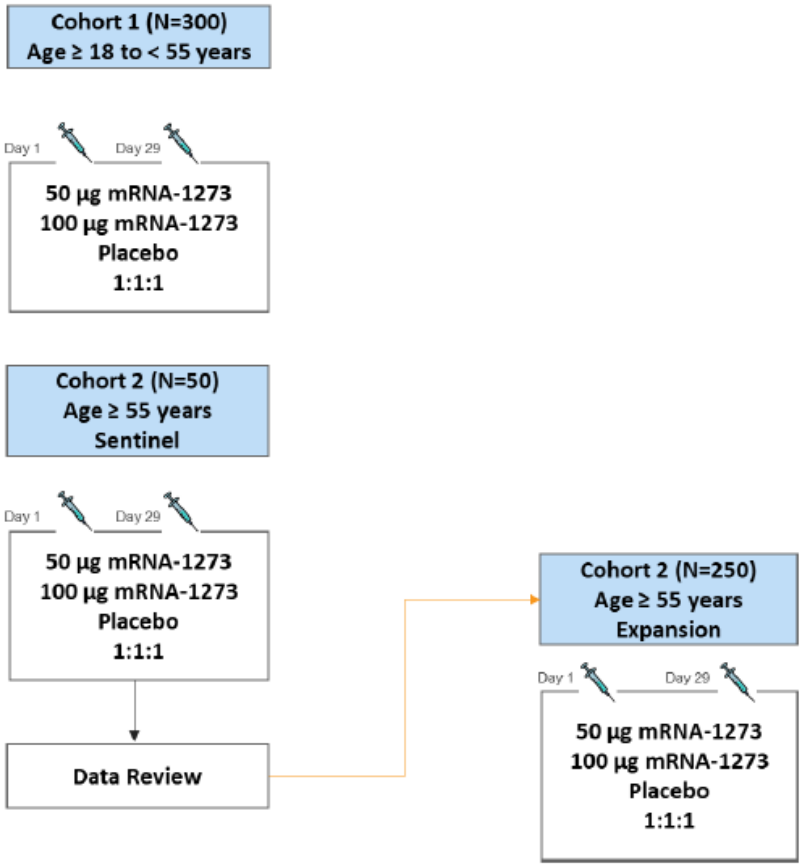


Figure 2: Sentinel and Expansion Cohort Schema



4.1.2. Part B, the Open-Label Interventional Phase

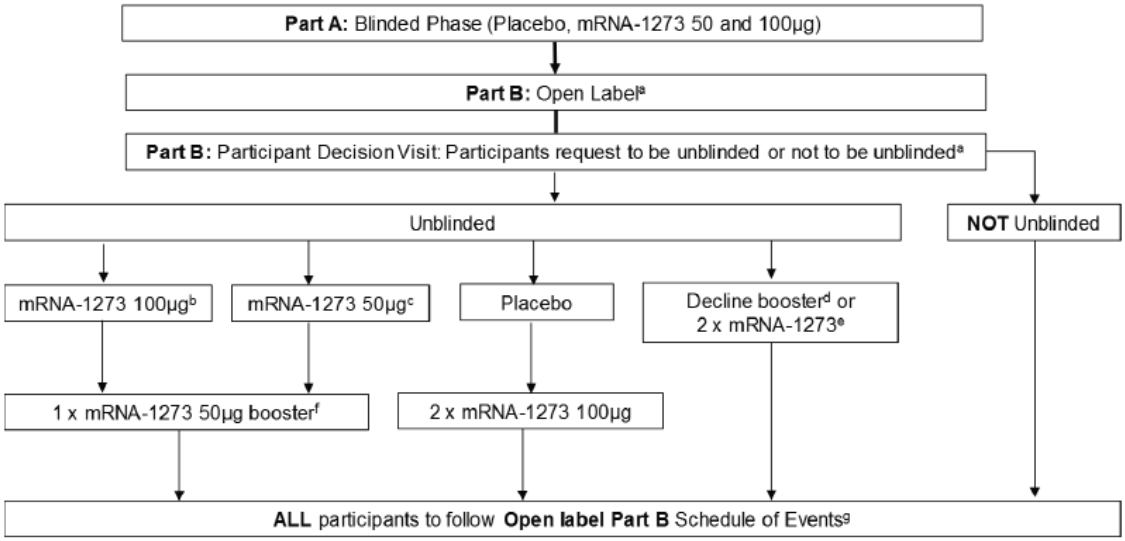
Part B, the Open-Label Interventional Phase of the study, is prompted by the authorization of a COVID-19 vaccine under an EUA. Transitioning the study to Part B permits all ongoing study participants to be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study participants an opportunity to schedule a Participant Decision Visit to know their original treatment assignment (placebo vs. mRNA-1273 [50 µg or 100 µg] vaccine).

Part B, the Open-Label Interventional Phase of the study, provides the opportunity for study participants who previously received placebo to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine. In addition, all participants who previously received 1 or 2 injections of mRNA-1273 (50 µg or 100 µg) vaccine will be able to receive a single booster dose of mRNA-1273 (50 µg). All study participants will receive a Notification

Letter summarizing the basis for a COVID-19 vaccine to receive an EUA and will be asked to schedule a Participant Decision Clinic Visit.

After the Participant Decision Clinic Visit (Protocol Table 10), all participants will proceed to the open-label Part B of the study and will follow the Part B Schedule of Events (Protocol Table 11 or Table 12) as follows (Figure 3).

Figure 3: Part B, Open-Label Schema



4.2. Sample Size and Power

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. Table 1 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. The 2-sided 95% CI is estimated (0.01%, 1.38%) at sample size of 400 with 1 participant reporting an AE. Furthermore, a sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Table 1: 95% Confidence Interval for One Participant with AE and the Lowest Detectable Incidence Rate at 95% Probability in Selected Sample Size

Sample Size Receiving mRNA-1273	Rate and 95% CI (%) at One Participant with AE			Lowest Detectible Rate (%) with ≥95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75

4.3. Randomization

There are two age cohorts in this study: participants ≥ 18 to < 55 years old in Cohort l and participants ≥ 55 years old in Cohort 2. Within each age cohort, approximately 300 participants will be randomized in 1:1:1 ratio to receive mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules.

4.4. Blinding and Unblinding

Part A of this study is observer-blind. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end or initiation of Part B, with certain exceptions, please refer to Section 3.4.5 of the protocol for details. There is a planned primary analysis when all subjects completed Day 57 Visit in Part A and a final analysis at end of study. At time of primary 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 or the initiation of Part B.

5. Analysis Populations

The following analysis sets are defined: Randomized Set, Solicited Safety Set, Safety set, Full Analysis set (FAS), and Per-Protocol (PP) set.

5.1. Randomized Set

The Randomized Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Subjects will be included in the vaccination group to which they were randomized.

5.2. Solicited Safety Set

Solicited Safety Set (Part A, Blinded Phase)

The Solicited Safety Set for Part A consists of all participants who are randomized and received any study injection during Part A, and contribute any solicited AR data, ie, have at least one post-baseline solicited safety assessment in Part A. The Solicited Safety Set will be used for the analyses of solicited ARs and subjects will be included in the vaccination group corresponding to the study injection they actually received during Part A. In addition, the following Solicited Safety Set is defined for each injection separately.

The First (Second) Injection Solicited Safety Set for Part A consists of all subjects in the Solicited Safety Set (Part A) who have received the first (second) study injection during Part A and have contributed any solicited AR data from the time of first (second) study injection through the following 6 days.

Subjects will be analyzed according to the vaccination group a subject received during Part A, rather than the vaccination group to which the subject was randomized. Subjects who receive a second injection that is different from the first injection will be summarized under the higher dose of vaccination group (eg, Placebo < mRNA-1273 50 μg < mRNA-1273 100 μg).

Solicited Safety Set (Part B, Open-Label Phase)

The Solicited Safety Set for Part B consists of all participants who are randomized in Part A and received any study injection during Part B, and contribute any solicited AR data, ie, have at least one post-baseline solicited safety assessment in Part B. The Solicited Safety Set will be used for the analyses of solicited ARs and subjects will be included in the vaccination group corresponding to the study injection they actually received in Part B, 100 μg of mRNA-1273 as 2 doses injection (for participants who received placebo injection in Part A) vs booster dose.

5.3. Safety Set

Safety Set (Part A, Blinded Phase)

The Safety Set for Part A consists of all randomized participants who received any study injection during Part A. The Safety Set for Part A will be used for analysis of safety except for the solicited ARs. Subjects will be included in the vaccination group corresponding to the vaccination they actually received in Part A. Subjects who receive a second injection that is different from the first injection will be summarized under the higher dose of vaccination group (eg, Placebo < mRNA-1273 50 μg < mRNA-1273 100 μg).

Safety Set (Part B, Open-Label Phase)

The Safety Set for Part B consists of all participants who are randomized in Part A and received any study injection during Part B. The Safety Set for Part B will be used for analysis of safety for Part B except for the solicited ARs. Subjects will be included in the vaccination group corresponding to the vaccination they actually received in Part B.

5.4. Immunogenicity Set (Part B, Open-Label Phase)

The Immunogenicity Set for Part B consists of all participants who were randomized in Part A and have at least one immunogenicity assessment for the Part B analysis endpoint.

Subjects will be included in the vaccination group to which they were assigned based on protocol specified criteria in Part B.

5.5. Full Analysis Set

Full Analysis Set (FAS) for SARS-CoV-2-specific bAb (Part A, Blinded Phase)

The FAS for SARS-CoV-2-specific bAb for Part A consists of all randomized participants who

a) receive any study vaccination during Part A, and

b) have baseline (Day 1) SARS-CoV-2-specific bAb data available, and

c) have at least one post-injection SARS-CoV-2-specific bAb assessment for the Part A analysis endpoint.

Subjects will be included in the vaccination group to which they were randomized.

FAS for SARS-CoV-2-specific nAb (Part A, Blinded Phase)

The FAS for SARS-CoV-2-specific nAb for Part A consists of all randomized participants who

a) receive any study vaccination during Part A, and

b) have baseline (Day 1) SARS-CoV-2-specific nAb data available, and

c) have at least one post-injection SARS-CoV-2-specific nAb assessment for the Part A analysis endpoint.

Subjects will be included in the vaccination group to which they were randomized.

FAS (Part B, Open-Label Phase)

The FAS for Part B consists of all randomized participants who

a) receive any study vaccination during Part B, and

b) have baseline (OL-Day 1) immunogenicity data available, and

c) have at least one post-injection immunogenicity assessment for the Part B analysis endpoint.

Subjects will be included in the vaccination group to which they were assigned based on protocol specified criteria in Part B.

5.6. Per-Protocol Set

Per-Protocol (PP) Set for SARS-CoV-2-specific bAb (Part A, Blinded Phase)

PP Set for SARS-CoV-2-specific bAb in Part A consists of all FAS for SARS-CoV-2-specific bAb for Part A subjects who meet all of the following criteria:

a) Complied with the injection schedule for Part A

b) Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective for SARS-CoV-2-specific bAb for Part A

c) Did not have SARS-CoV-2 infection at baseline for Part A

d) Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective in Part A

The PP Set for SARS-CoV-2-specific bAb for Part A will serve as the primary population for the analysis of SARS-CoV-2-specific bAb immunogenicity data in Part A.

Subjects will be included in the vaccination group to which they were randomized.

PP Set for SARS-CoV-2-specific nAb (Part A, Blinded Phase)

PP Set for SARS-CoV-2-specific nAb for Part A consists of all FAS for SARS-CoV-2-specific nAb for Part A subjects who meet all of the following criteria:

a) Complied with the injection schedule in Part A

b) Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective for SARS-CoV-2-specific nAb for Part A

c) Did not have SARS-CoV-2 infection at baseline for Part A

d) Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective in Part A

The PP Set for SARS-CoV-2-specific nAb for Part A will serve as the primary population for the analysis of SARS-CoV-2-specific nAb data in Part A.

Subjects will be included in the vaccination group to which they were randomized.

PP Set (Part B, Open-Label Phase)

PP Set for Part B consists of all FAS for Part B subjects who meet all of the following criteria:

a) Complied with the injection schedule in Part B

b) Had post-injection immunogenicity assessment at timepoint of primary interest for the Part B immunogenicity analysis

c) Did not have SARS-CoV-2 infection at OL-Day 1 for Part B, where SARS-CoV-2 infection 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 (as measured by Roche Elecsys Anti- SARS-CoV-2 assay).

d) Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective in Part B

The PP Set for Part B will serve as the primary population for the analysis of immunogenicity data in for Part B.

Subjects will be included in the vaccination group to which they were assigned based on protocol specified criteria in Part B.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in the protocol Table 9 for Part A Blinded Phase, Table 11 and Table 12 for Part B Open-Label Phase.

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).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study injection. For safety tests (Part B), the baseline is defined as the non-missing measurement collected on OL-Day 1 and before the first dose of study injection in Part B. For immunogenicity tests (Part A) 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 study injection (Day 1). For immunogenicity tests (Part B) the baseline is defined as the non-missing measurement collected in Part B and before or on the date of first dose of injection in Part B (OL-Day 1).

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.

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 age cohort and vaccination group within the analysis set of interest, unless otherwise specified.

Study day relative to the first injection in Part A 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 in Part A;

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

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

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

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

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

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

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

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

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

e) study day on or after the date of the second injection in Part B will be calculated as: date of assessment/event – date of the second injection in Part B + 1; if study day is on the same day as the second injection in Part B, date and time will be compared

with the second injection date and time in Part B. If it is prior to the second injection in Part B, then study day is calculated as d); If it is after the second injection in Part B or the time is missing or not available then study day is calculated as: date of assessment/event – date of the second injection in Part B + 1.

For calculation regarding antibody levels/titers:

Part A:

Antibody values reported as below the 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. Missing results will not be imputed.

Part B:

Antibody values reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the ULOQ and without actual values reported (eg, '>xxx') will be converted to the ULOQ. Values that are greater than the ULOQ and with actual values reported will not be imputed. Missing results will not be imputed.

This study can be divided into the following **stages**:

- Vaccination stage:

  Part A:

  For assessments that will be collected throughout the study (eg, unsolicited AE), it consists first injection on Day 1 to 28 days after last injection in Part A (ie, the day of last injection and 27 subsequent days).

  For assessments that will be collected at study visits (eg. laboratory and vital sign), if a subject receives two injections, this stage starts at the first injection on Day 1 and continues through Month 2 visit; If a subject receives first injection only, this stage starts at the first injection on Day 1 and continues through Month 1 visit.

  Part B:

  For assessments that will be collected throughout the study (eg, unsolicited AE), it consists first injection on OL-Day 1 to 28 days after last injection in Part B (ie, the day of last injection and 27 subsequent days).

  For assessments that will be collected at study visits (eg. laboratory and vital sign), if a subject receives two injections, this stage starts at the first injection on

OL-Day 1 and continues through OL-M2 visit; If a subject receives first injection only, this stage starts at the first injection on OL-Day 1 and continues through OL-M1 visit.

- Follow up stage:

  Subjects who did not receive dose in Part B:

  Consists of all periods that begin 28 days after the last injection in Part A (ie, the day of last injection in Part A + 28 days, regardless of number of injections received) and continue until the earliest date of (study completion, discontinuation from the study, or death).

  Subjects who received dose in Part B:

  Consists of all periods that begin 28 days after the last injection in Part A (ie, the day of last injection in Part A + 28 days, regardless of number of injections received) and continue until the earliest date of first injection in Part B, and all periods that begin 28 days after the last injection in Part B (ie, the day of last injection in Part B + 28 days, regardless of number of injections received) and continue until the earliest date of (study completion, discontinuation from the study, or death).

- Day 1 to End of Study: Begins at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).
- 28 days after any vaccination stage: 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)).

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 (eg, <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 (eg, >3000), the numeric values will be imputed by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

The following vaccination **groups** will be used for summary purposes:

- Part A, Blinded Phase:
    - mRNA-1273 50 µg
    - mRNA-1273 100 µg
    - mRNA-1273 Total
    - Placebo
- Part B, Open-Label Phase:
    - mRNA-1273 50 µg - Booster
    - mRNA-1273 100 µg - Booster
    - mRNA-1273 - Booster Total
    - Placebo - mRNA-1273

If a subject received any study vaccination injection that is at a non-protocol dose in Part A, the subject will be assigned to a protocol dose (Placebo, mRNA-1273 vaccine 50 µg, or mRNA-1273 vaccine 100 µg) for that injection according to the following rule:

- mRNA-1273 50 µg if the received dose > 0 µg and <= 75 µg, or
- mRNA-1273 100 µg if the received dose > 75 µg

Summary by age cohort:

All analyses and data summaries/displays will be provided by vaccination group for overall (the 2 age cohorts combined) and for each age cohort (>= 18 to < 55 years old, >= 55 years old), unless otherwise specified.

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 age cohort and vaccination group as defined in Section 6.1 based on the Randomized Set for Part A and the Part B Safety Set for Part B:

- Randomized Set
- Solicited Safety Set (Part A and Part B)
- Safety Set (Part A and Part B)
- Full Analysis Set (Part A and Part B)
- PP Set (Part A and Part B)

The percentage will be based on subjects in that age cohort and vaccination group within the Randomized Set for Part A and within the Part B Safety Set for Part B.

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 age cohort and vaccination group based on the Randomized Set:

- Randomized by site
- Received each study vaccine during Part A

- Prematurely discontinued study vaccine during Part A and the reason for discontinuation
- Consented to Part B
- Agreed to be unblinded
- Agreed to receive mRNA-1273 in Part B
- Received each study vaccine during Part B
- Prematurely discontinued study vaccine during Part B and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

The denominator for all percentages will be the number of subjects in that age cohort and vaccination group within the Randomized Set for Part A and within the Part A Safety Set for Part B.

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 subject disposition listing will be provided for Part B, including unblinding status at Part B, subjects who received mRNA-1273 in Part B, subjects who completed the study injection schedule in Part B, subjects who discontinued from study vaccine in Part B, 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 in Part A or the initiation of Part B, whichever is earlier, is considered to have completed Part A of the study.

A subject who completed OL-M6 or OL-M7 relative to the number of injections received in Part B is considered to have completed Part B of the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of subjects will be provided for categorical variables such

as gender, race, ethnicity. The summaries will be presented by age cohort and vaccination group as defined in Section 6.1 based on the Safety Set, PP Set and FAS for Part A and Part B separately. If the Safety Set differs from the Randomized Set (eg, subjects randomized but not received any study injection; subjects received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomized Set. If the FAS for SARS-CoV-2-specific bAb and the FAS for SARS-CoV-2-specific nAb are the same, only one table will be provided. Otherwise, this will be generated for both the FAS for SARS-CoV-2-specific bAb and FAS for SARS-CoV-2-specific nAb. Same rule applies to the PP Set for SARS-CoV-2-specific bAb, PP Set for SARS-CoV-2-specific nAb. For Part B, if the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, tables will be provided for both FAS and PP Set, otherwise, only one table will be provided for the PP set.

For screened failure subjects, age (years), 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 the Safety Set for Part A. 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 total mRNA-1273 and then alphabetically within SOC.

Medical history data 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 for Part A and Part B separately.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (ie, on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (ie, on the day of injection and the 27 subsequent days) will be summarized by age cohort and 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
- Prophylactic antipyretics or analgesics medication within 28 Days Post Injection
- Antipyretic or analgesic medication within 28 Days Post Injection

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the first injection in Part A or Part B through 28 days after the last injection in Part A or Part B will be provided by PT in descending frequency in the mRNA-1273 group with both dose level combined.

Medications taken to prevent pain or fever will be collected on eDiary and summaries will be provided for Part A and Part B separately based on the Solicited Safety Set by age cohort and vaccination group as defined in Section 6.1 for each injection (first or second) and any injection, including within 7 days after injection, beyond 7 days after injection and after injection.

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

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study vaccine administration data will be presented in a listing.

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 developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by age cohort and vaccination group as defined in Section 6.1 based on the Randomized Set for Part A and within the Part B Safety Set for Part B.

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, AEs leading to withdrawal from study vaccine and/or study participation, safety laboratory test results, vital signs, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA. 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 with modifications for rash as presented in Table 6 from protocol.

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

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 age cohort and vaccination group for Part A and Part B separately unless otherwise specified.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event not present 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 age cohort, vaccination group, and stage (28 days after any vaccination stage for Part A and Part B separately, and Day1 to End of 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 TEAEs 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 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 (of related AEs), 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.

6.3.1.1. Incidence of Adverse Events

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

- Any unsolicited TEAEs
- Any serious TEAEs
- Any unsolicited TEAEs that are medically-attended
- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited Severe TEAEs
- Any unsolicited TEAEs that are fatal

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

In addition, separate listings containing individual subject adverse event data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, and unsolicited medically-attended AEs will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

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

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited TEAEs that are medically-attended

6.3.1.3.TEAEs by Preferred Term

A summary table of all unsolicited TEAEs will be provided. PTs will be sorted in a descending order according to the frequency in mRNA-1273 vaccine Total column.

6.3.1.4.TEAEs by System Organ Class, Preferred Term and Severity

The following summary tables of TEAEs will be provided by SOC, PT, and severity (mild, moderate, and severe) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.3.2. Solicited Adverse Reactions

6.3.2.1.Analysis of Reactogenicity

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. Any new safety information reported during safety telephone calls or at site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF (and marked as "Yes" to the AE eCRF question "Was this a solicited adverse reaction?"), and will be included in the evaluation of solicited ARs in addition to the eDiary data.

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 (ie, solicited ARs).

The following local ARs will be solicited: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, fever, and chills.

The solicited ARs will be graded based on the grading scales presented in Table 6 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 the Grading for rash and Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution.

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

All solicited ARs analyses will be based on the Solicited Safety Set. All solicited ARs analyses will be provided by age cohort and vaccination group as defined in Section 6.1 for each injection (first or second) (Part A only) and any injection (Part A and Part B separately), unless otherwise specified.

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

percentage of subjects who reported each individual solicited AR will also be summarized by age cohort, vaccination group, severity grade, day of reporting and injection. The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by severity grade will be provided.

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 summary by age cohort, vaccination group, study day relative to the corresponding injection (Day 1 through Day 7), and injection.

The number of days reporting each solicited AR will be summarized descriptively and for the following time windows (1-2 days, 3-4 days, 5-6 days, and >=7 days) by age cohort, vaccination group, and injection. The number of days will be calculated as the days of the solicited AR is reported within the 7 days of injection including the day of injection, no matter it is intermittent or continued. If the solicited AR continues beyond 7 days, the consecutive days a solicited AR is reported after 7 days will be included (eg, an event that lasted 5 days in the first 7 days post injection and 3 consecutive days beyond 7 days post injection, the duration will be reported as 8 (5+3) days.)

The number and percentage of subjects who reported solicited rash and lymphadenopathy assessed by healthcare provider will be summarized by age cohort, vaccination group, severity grade, and injection.

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

6.3.2.2.Compliance of eDiary

Solicited ARs will be recorded in an eDiary on the day of each vaccine administration and for the 6 days after the day of injection. The completion status of the eDiaries among the 7-day period and on each individual day will be summarized.

6.3.3. Clinical Laboratory Evaluations

Safety laboratory testing will be performed in Part A of the study and will include hematology, serum chemistry, coagulation, and pregnancy test.

A pregnancy test will be performed on all female subjects of childbearing potential at the Screening Visit and before each vaccine administration (Day 1 and Day 29) via point-of-care urine, and as needed at unscheduled visits (urine or serum pregnancy test based on the Investigator's discretion).

All laboratory test results, including screening safety laboratory tests for Cohort 1 and Cohort 2 subjects and post-baseline tests for Cohort 2 subjects, will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the toxicity grading criteria in any safety laboratory (hematology, serum chemistry and coagulation) will be listed separately. If a subject has an abnormal laboratory test at any post injection visit, then all results for that subject and laboratory test will be presented in the listing.

For continuous hematology, serum chemistry, and coagulation measurements, the observed values and changes from baseline will be summarized at each visit by vaccination group as defined in Section 6.1 for Cohort 2. The number and percentage who had any abnormal result based on toxicity grades in hematology, serum chemistry, or coagulation measurements will also be summarized by visit and vaccination group for Cohort 2. Shift from baseline in the toxicity grades to the worst post-baseline result in the vaccination stage will also be summarized by vaccination group for Cohort 2.

6.3.4. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 2 or higher abnormality at any post injection visit, then all results of vital sign measurement for that subject will be presented in the listing.

Observed values and changes from baseline for all vital sign measurements will be summarized at each visit by age cohort and vaccination group as defined in Section 6.1 for Part A and Part B separately. Shift from baseline in the toxicity grades at each visit and

shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized by age cohort and vaccination group for Part A and Part B separately.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Set and will be performed by vaccination group as defined in Section 6.1. for each age cohort, and for Part A and Part B separately, as applicable. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10% (for each age cohort), supportive analyses of immunogenicity may be conducted using the FAS. The supportive analysis is required if the condition is met.

The GMT and geometric mean (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 titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers 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 titers or levels for subject *i* at time points *j* and *k*, $j \neq k$

Seroresponse at a participant level is defined as below in Table 2.

Table 2 Seroresponse

Category	Test Name	Definition Seroresponse
nAb	Pseudovirus Neutralizing Antibody ID50 Titers	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-fold-rise
	Pseudovirus Neutralizing	baseline <LLOQ: >=LLOQ

	Antibody ID80 Titers	baseline >=LLOQ: 2.3- fold-rise
bAb (ELISA)	VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6- fold-rise
bAb (Meso scale discoversy [MSD] MULTIPLEX)	SARSCOV2SP	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9- fold-rise
	All other tests	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4- fold-rise (unless specified otherwise)

6.4.1. Immunogenicity Assessments

There will be two types of immunogenicity assessments:

- Serum bAb level against SARS-CoV-2 as measured by ELISA specific to the SARS-CoV-2 S protein
- Serum bAb level against SARS-CoV-2 as measured by MSD specific to the SARS-CoV-2 S protein (Part B)
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

6.4.2. Analysis of Antibody-Mediated Immunogenicity Endpoints

For each group, the following evaluations will be performed at each time point at which blood samples are collected for immunogenicity (unless otherwise specified):

- GM level of SARS-CoV-2-specific bAb levels 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. GM level and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.
- GM fold-rise of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1 for Part A and at OL-Day 1 for Part B. 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. GM fold-rise and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

- For VAC65 spike IgG antibody test in Part A and all bAb tests in Part B, proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific bAb levels from OL-Day 1 (baseline) at each post-injection time points will be tabulated with 2-sided 95% Clopper-Pearson CIs.
- For VAC65 spike IgG antibody test in Part A and all bAb tests in Part B, proportion of subjects with seroconversion in serum SARS-CoV-2-specific bAb will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint. Seroconversion in serum SARS-CoV-2-specific bAb at a participant level is defined as a change of bAb level from below the LLOQ to equal to or above LLOQ, or a 4-times higher titer ratio in participants with pre-existing bAb levels.
- For VAC65 spike IgG antibody test in Part A and all bAb tests in Part B, proportion of subjects with seroresponse (as defined in Table 2) for bAb will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint.
- GMT of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each time point using the same method mentioned above.
- GMFR of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1 for Part A and at OL-Day 1 for Part B using the same method mentioned above.
- Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers from Day 1 (baseline) at each post-injection time points in Part A and from OL-Day 1 (baseline) at each post-injection time points in Part B will be tabulated with 2-sided 95% Clopper-Pearson CIs.
- Proportion of subjects with seroconversion in serum SARS-CoV-2-specific nAb will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint for Part A and Part B respectively. Seroconversion in serum SARS-CoV-2-specific nAb at a participant level is defined as a change of nAb titer from below the LLOQ to equal to or above LLOQ, or a 4-times higher titer ratio in participants with pre-existing nAb titers.

- For Part B, proportion of subjects with seroresponse (as defined in Table 2) for nAb will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint.
- GM level, GMT and GMFR with corresponding 95% CI will also be evaluated using an ANCOVA model with baseline level/titer as a covariate and age cohort as a factor in the analysis in the overall group. The model will be conducted based on the log-transformed values then back transformed to the original scale for presentation.
- Per the study protocol, if the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. Additional sensitivity analysis of immunogenicity data may be conducted for the above endpoints using the "Adjusted" Per-protocol Set based on the more rigid visit window, -3/+7 for Day 29 visit, as appropriate.

6.5. Exploratory Analysis

6.5.1. Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- Descriptive summaries of the relative proportions of S protein-specific serum Igs and nAb during the study. Subclass analysis of specific immunoglobulin G (IgG) may be performed.
- Titers of bAb and nAb in serum following the first dose (Day 1) and prior to the second dose (Day 29).
- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study. The analysis may not be included in the Clinical Study Report (CSR).
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.
- Exploratory analysis comparing each dose level of mRNA-1273 versus placebo on bAb and nAb.

6.5.2. Nasopharyngeal Swab Assessments

Nasopharyngeal swab samples will be collected for SARS-CoV-2 testing. The number and percentage of subjects with detected and not detected will be summarized at each visit by age cohort and vaccination group as defined in Section 6.1 for Part A and Part B separately.

6.5.3. SARS-CoV-2 Exposure and Symptoms

SARS-CoV-2 reported exposure history and symptoms assessment will be assessed during the study.

The number and percentage of subjects who had close contact with a person with SARS-CoV-2 infection or COVID-19, reasons for exposure, subjects with any symptoms of potential COVID-19, and subjects with each symptoms will be presented by visit, age cohort, and vaccination group as defined in Section 6.1. Descriptive statistics will be provided for length of exposure in days and time from exposure to first symptom by age cohort and vaccination group.

In addition, the following listings will be provided for subjects infected by SARS-CoV-2:

- Serum bAb level against SARS-CoV-2
- Serum nAb titer against SARS-CoV-2
- Solicited ARs
- Unsolicited AEs

6.6. Planned Analyses

6.6.1. Primary Study Analysis for Blinded Part A Only

A primary analysis of safety and immunogenicity data will be performed after participants have completed Day 57 study procedures. This primary analysis may be performed when all participants in Cohort 1 and the Cohort 2 sentinel group have completed Day 57 study procedures and/or when all participants in Cohort 1 and Cohort 2 have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (as clean as possible) and locked. A limited number of Sponsor and clinical research organization (CRO) personnel will be unblinded to perform the primary study analysis and prepare a final CSR.

An independent, unblinded statistics team will carry out the primary analysis. The unblinded statistics team will not be involved in either study design or the regular study

conduct. The study site staff, investigators, study monitors, and participants will remain blinded until the initiation of Open-Label Part B.

6.6.2. Analysis at End of Blinded Part A Only

An analysis of safety and immunogenicity data will be performed after all participants have completed Part A of the study. All data collected in Part A of the study will be cleaned (ie, data that are as clean as possible) and locked and a report may be generated as needed.

6.6.3. Interim Analyses for Open-Label Prat B Only

Interim analyses of the safety and immunogenicity data may be performed after participants have completed the OL-Day 29 and/or the OL-Day 57 study procedures. This analysis may be performed when all participants have completed OL-Day 29 and/or OL-Day 57 study procedures, or on a subset of participants who received a single booster dose at OL-Day 1 when they have completed OL-Day 29 and/or OL-Day 57 study procedures. All data collected in Part B of the study will be cleaned (ie, data that are as clean as possible) and locked and a report may be generated as needed. Results of this analysis may be presented in a CSR.

6.6.4. Additional Study Analyses

Additional analyses may be performed to support regulatory request as appropriate.

6.6.5. Final Analysis at End of Part B

The final analysis of all endpoints for Open-Label Part B will be performed after all participants have completed OL-M6 and OL-M7 respectively (Open-Label Part B) study procedures and after the database is cleaned and locked. All data collected from the initiation of Part B to End of Part B will be included in this analysis. Results of this analysis will be presented in an end of study CSR, including individual listings.

6.7. Safety Monitoring Committee (SMC) Review

There is one planned safety review by the Safety Monitoring Committee (SMC) consists of external experts. Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the SPONSOR and designated CRO study team; and requirements for the proper documentation of SMC minutes will be described in a separate charter that will be reviewed and approved by the SMC.

7. Changes from Planned Analyses in Protocol

Section	Planned Analysis in Protocol	Analysis in SAP
6.1 General Consideration	Antibody values reported as below the limit of detection or LLOQ will be replaced by 0.5 × limit of detection or 0.5 × LLOQ.	Antibody values reported as below LLOQ will be replaced by 0.5 × LLOQ.
6.4 Immunogenicity Analysis	Seroconversion at a participant level is defined as a change of nAb titer from below the limit of detection or LLOQ to equal to or above limit of detection or LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers.	Seroconversion at a participant level is defined as a change of nAb titer from below the LLOQ to equal to or above LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers.

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. September 2007 [cited 2019 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 Safety and Immunogenicity 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.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity 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
Labs		
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43]
Day 57 (Month 2)	57	≥44 and prior to Participant Decision Visit

Nasal Swabs for SARS-CoV-2		
Baseline	1 (Date of First Injection)	≤1
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43]
Day 57 (Month 2)	57	[44, 70]
Day 71 or Beyond	71	≥71 and prior to Participant Decision Visit
Baseline (OL-Day 1)	1 (Date of First Injection on OL-Day 1) relative to OL-Day 1	≤1 and VISIT is OL-Day 1
OL-Day 29	29 (Date of Second Injection in Part B) relative to OL-Day 1	[2, 43]
OL-Day 57	57 relative to OL-Day 1	[44, 70]
OL-Day 71 or Beyond	71 relative to OL-Day 1	≥71
Vital Signs		
Day 8	8	[2, 11]
Day 15	15	[12, 22]
Day 29 (Month 1)	29 (Date of Second Injection)	[23, 32]
Day 36	36	[33, 39]
Day 43	43	[40, 50]
Day 57 (Month 2)	57	[51, 133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302 and prior to Participant Decision Visit
Baseline (OL-Day 1)	1 (Date of First Injection on OL-Day 1) relative to OL-Day 1	≤1 and VISIT is OL-Day 1
OL-Day 29	29 (Date of Second Injection in Part B) relative to OL-Day 1	[2, 43]
OL-Day 57 for subjects receiving 2 doses in Part B	57 relative to OL-Day 1	[44, 133]
OL-Day 209 for subjects receiving 2 doses in Part B	209 relative to OL-Day 1	≥134
OL-Day 57 for subjects receiving 1 dose in Part B	57 relative to OL-Day 1	[44, 119]

OL-Day 181 for subjects receiving 1 dose in Part B	181 relative to OL-Day 1	≥120
Immunogenicity		
Baseline	1 (Date of First Injection)	≤1
Day 15	15	[2, 22]
Day 29 (Month 1)	29 (Date of Second Injection)	[23, 36]
Day 43	43	[37, 50]
Day 57 (Month 2)	57	[51,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302 and prior to Participant Decision Visit
Baseline (OL-Day 1)	1 (Date of First Injection on OL-Day 1) relative to OL-Day 1	≤1 and VISIT is OL-Day 1
OL-Day 8	8 relative to OL-Day 1	[2, 11]
OL-Day 15	15 relative to OL-Day 1	[12, 22]
OL-Day 29 (Month 1)	29 (Date of Second Injection) relative to OL-Day 1	[23, 43]
OL-Day 57 for subjects receiving 2 doses in Part B	57 relative to OL-Day 1	[44, 133]
OL-Day 209 for subjects receiving 2 doses in Part B	209 relative to OL-Day 1	≥134
OL-Day 57 for subjects receiving 1 dose in Part B	57 relative to OL-Day 1	[44, 119]
OL-Day 181 for subjects receiving 1 dose in Part B	181 relative to OL-Day 1	≥120

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

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 CM end date is after the date of first injection or is missing AND the start month and year of the CM 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 CM end date is after the date of first injection or is missing AND the start year of the CM 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 a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Injection**	**≥ First Dose Date and ≤ End Date of Last Study Injection in each Part + 27 days**	**> 27 Days After Last Injection in each Part [2]**
< First dose date of study vaccination [1]	P	PC	PCA
≥ First dose date and ≤ 27 days after last injection in each Part	-	C	CA
> 27 days after last injection in each Part	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

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:

3. 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.

4. Missing or partial AE end dates will not be imputed.

9.5. Appendix E: Schedule of Events

Please refer to Table 9 for Part A Blinded Phase, Table 11 and Table 12 for Part B Open-Label Phase in Appendix 1 Schedule of Events in the protocol.

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTX, Inc.**
Protocol Number:	**mRNA-1273-P201**

Document Description:	Statistical Analysis Plan
SAP Title:	A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
SAP Version Number:	4.0
Effective Date:	03 June 2021

Author(s):

For PPD: Yu Feng, Principal Biostatistician

Approved by:

DocuSigned by:
Roderick McPhee
Signer Name: Roderick McPhee
Signing Reason: I approve this document
Signing Time: 04-Jun-2021 | 08:04 EDT
9E507B7350DB40489785217A4012E0B1

04-Jun-2021 | 08:05 EDT

Roderick McPhee , MD
Director, Clinical Development Infectious Diseases
Moderna, Inc.

Date *(DD-MMM-YYYY)*

DocuSigned by:
Honghong Zhou
Signer Name: Honghong Zhou
Signing Reason: I approve this document
Signing Time: 03-Jun-2021 | 21:15 EDT
571812603E6F4BB7B85B8C5B9EDBA2A9

03-Jun-2021 | 21:15 EDT

Honghong Zhou, PhD
Senior Director, Biostatistics
Moderna, Inc.

Date *(DD-MMM-YYYY)*

DocuSigned by:
Wenmei Huang
Signer Name: Wenmei Huang
Signing Reason: I approve this document
Signing Time: 03-Jun-2021 | 21:10 EDT
78AB3517B9A348A79A38E6D911A91E95

03-Jun-2021 | 21:11 EDT

Wenmei Huang, PhD
Senior Director, Biostatistics
Moderna, Inc.

Date (DD-MMM-YYYY)