16.1.9 Documentation of Statistical Methods

This section contains the following documents:

Statistical Analysis Plan Amendment 1, Part A. Version 2.0, dated 08 March 2021

ModernaTX, Inc.

Protocol mRNA-1273-P301

A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Statistical Analysis Plan
Amendment 1, Part A

SAP Version 2.0
Version Date of SAP: 08 March 2021

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	10 September 2020	Original Version (Version 1.0)
2.0	08 March 2021	Amendment 1 (Version 2.0) • Updated SAP for final blinded analysis based on blinded data after protocol amendment 6 that offers participants opportunities to be unblinded and to receive mRNA-1273 for those who were randomized to Placebo • Updated overall study design based on protocol amendment 6 • Updated Section 6.3.1 and 6.3.2 on derivation of efficacy endpoints to clarify how scheduled RT-PCR and bAb specific to SARS-CoV-2 NP at scheduled timepoints will be considered for disease efficacy endpoints • Updated Section 6.3.2.2 on analysis of vaccine efficacy to prevent asymptomatic SARS-CoV-2 infection • Analysis of exploratory objective VE against all-cause mortality was moved from Section 6.3.2.2. to Section 6.8.4. • Added Section 6.4.2 to describe the analyses that have been conducted to date for the P301 study • Added Section 6.6.1.6 • Updated Section 6.7 to include sampling plan for immunogenicity, update immunogenicity data and analyses planned to characterize immunogenicity of mRNA-1273

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
ARDS	acute respiratory distress syndrome
bAb	binding antibody
BARDA	Biomedical Advanced Research and Development Authority
BMI	body mass index
BOD	burden of disease
BOI	burden of infection
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
DHHS	Department of Health and Human Services
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HR	hazard ratio

Abbreviation	Definition
ICH	International Council for Harmonisation
IP	investigational product
IRT	interactive response technology
LOD	limit of detection
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
PDV	Participant Decision Visit
PH	proportional hazard
PP	per-protocol
PT	preferred term
REML	restricted (or residual, or reduced) maximum likelihood
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
VE	vaccine efficacy
WHO	World Health Organization

Abbreviation	Definition
WHODD	World Health Organization drug dictionary

1. Introduction

The previously approved SAP version 1.0, dated 08-September-2020 described the planned analyses for Study mRNA-1273-P301. SAP version 1.0 was based on the clinical study protocol (CSP) Amendment 3, dated 20-August-2020, and electronic case report form (eCRF) Version 2.026, dated 21-AUG-2020. SAP version 1.0 was finalized and approved prior to the planned first interim analysis (IA1, data snapshot 1 occurred on 11-November-2020). Primary efficacy objective based on COVID-19 was demonstrated based on pre-defined statistical criterion at the first interim analysis. The primary analysis of efficacy was performed based on Data Snapshot 2 (25-November-2020) with the total number of COVID-19 cases based on adjudication committee assessment > 151, the target total number of events at the originally planned primary analysis (Section 9.6 of the protocol). The results based on IA1 (DS1, 11-NOV-2020) and Primary analysis (DS2, 25-NOV-2020) served as the basis for application of mRNA-1273 for Emergency Use Authorization (EUA).

This statistical analysis plan (SAP), version 2.0, is based on clinical study protocol (CSP) Amendment 6, dated 23-December-2020 and the approved electronic case report form (eCRF) Version 9.015, dated 04-FEB-2021. The CSP Amendment 6 informs all ongoing study participants of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and offers participants who originally received placebo in this study the potential benefit of vaccination against COVID-19, given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met per the protocol-defined interim analysis.

This SAP Amendment 1 (Part A) focuses on the blinded phase of the study, and a separate SAP (Part B) will be provided for the unblinded phase analyses not covered in this SAP. A final blinded efficacy analysis is planned to provide final efficacy update based on data from the blinded phase of the study when approximately 90% of the study participants have had the participant decision visit or have been unblinded or discontinued from the study. Unless specified otherwise, the language in this SAP pertains to Part A.

The updates in SAP version 2.0 are summarized in Document History.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9) 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 which are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P301 is a Phase 3, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of messenger ribonucleic acid (mRNA)-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis; Statistical Analysis System (SAS) Version 9.4 or higher will be used, and R or RStudio may be used. SAP version 1.0, dated 08-September-2020 was finalized and approved prior to the first interim 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.

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

2. Study Objectives

2.1. Primary Objectives

2.1.1. Primary Efficacy Objective

The primary efficacy objective is to demonstrate the efficacy of mRNA-1273 to prevent COVID-19.

2.1.2. Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.

2.2. Secondary Objectives

2.2.1. Secondary Efficacy Objectives

The secondary efficacy objectives are:

- To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.
- To evaluate vaccine efficacy (VE) against a secondary definition of COVID-19.
- To evaluate VE to prevent death caused by COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first injection.
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.
- To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.

2.2.2. Secondary Immunogenicity Objective

The secondary immunogenicity objective is to evaluate the immunogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.

2.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of mRNA-1273 on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by reverse transcription polymerase chain reaction (RT-PCR) and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR.
- To assess VE to reduce the duration of symptoms of COVID-19.
- To evaluate VE against all-cause mortality.
- To assess VE against burden of disease (BOD) due to COVID-19.
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
- To evaluate immune response markers after dosing with IP as correlates of risk of COVID-19 and as correlates of risk of SARS-CoV-2 infection.
- To conduct additional analyses related to furthering the understanding of SARS-CoV-2 infection and COVID-19, including analyses related to immunology, this or other vaccines, detection of viral infection, and clinical conduct.

3. Study Endpoints

3.1. Primary Endpoints

3.1.1. Primary Efficacy Endpoint

The primary efficacy objective will be evaluated by the VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second injection of IP, where COVID-19 is defined as symptomatic disease based on the following criteria:

- The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR

- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

3.1.2. Primary Safety Endpoint

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 of IP (Part A: Blinded Phase only).
- Unsolicited adverse events (AEs) through 28 days after each injection of IP (Part A: Blinded Phase only).
- Medically-attended AEs (MAAEs) or AEs leading to withdrawal through the entire study period.
- Serious AEs (SAEs) throughout the entire study period.

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints

The secondary efficacy objectives will be evaluated by the following endpoints:

- The VE of mRNA-1273 to prevent severe COVID-19, defined as first occurrence of COVID-19 starting 14 days after the second injection of IP, (as per the primary endpoint) AND any of the following:
    - Clinical signs indicative of severe systemic illness, Respiratory Rates ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FIO_2 < 300$ mm Hg, OR

  - Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
  - Significant acute renal, hepatic or neurologic dysfunction, OR
  - Admission to an intensive care unit or death.

- The VE of mRNA-1273 to prevent the first occurrence of either COVID-19 or SARS-CoV-2 infection starting 14 days after the second injection of IP. This endpoint is a combination of COVID-19 (primary endpoint or secondary definition of COVID-19 cases) and asymptomatic SARS-CoV-2 infection assessed by seroconversion, for participants with negative SARS-CoV-2 status at baseline.
- The VE of mRNA-1273 to prevent the secondary case definition of COVID-19 starting 14 days after the second injection of IP. The secondary case definition of COVID-19 is defined as at least one of the following systemic symptoms: fever (temperature ≥ 38ºC), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
- The VE of mRNA-1273 to prevent death due to a cause directly attributed to a complication of COVID-19, starting 14 days after the second injection of IP.
- The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the first injection of IP.
- The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second injection of IP regardless of evidence of prior SARS-CoV-2 infection determined by serologic titer against SARS-CoV-2 nucleocapsid or RT-PCR at baseline.

- The VE to prevent the first occurrence of SARS-CoV-2 infection in the absence of symptoms defining COVID-19 starting 14 days after the second injection of IP. SARS-CoV-2 infection will be assessed by seroconversion and with a negative NP swab sample for SARS-CoV-2 at Day 1.

3.2.2. Secondary Immunogenicity Endpoints

The secondary immunogenicity objective will be evaluated by the following endpoints:

- Geometric mean titer (GMT) of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759.
- Geometric mean fold rise (GMFR) of SARS-CoV-2-specific nAb relative to Day 1 on Day 29, Day 57, Day 209, Day 394, and Day 759.
- Quantified levels or GMT of S protein-specific binding antibody (bAb) on Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759.
- GMFR of S protein-specific bAb relative to Day 1 on Day 29, Day 57, Day 209, Day 394, and Day 759.

3.3. Exploratory Endpoints

The exploratory endpoints of the study are:

- The VE of mRNA-1273 on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by RT-PCR and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR
- The VE of mRNA-1273 to reduce duration of COVID-19 symptoms
- The VE of mRNA-1273 against BOD based on the post SARS-CoV-2 infection follow-up
- The VE of mRNA-1273 against all-cause mortality

- The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence
- Immune response markers after dosing with IP as correlates of risk of COVID-19 and as correlates of risk of SARS-CoV-2 infection
- Additional analyses related to furthering the understanding of SARS-CoV-2 infection and COVID-19, including analyses related to the immunology of this or other vaccines, detection of viral infection, and clinical conduct

4. Study Design

4.1. Overall Study Design

This is a two-part Phase 3 study: Part A and Part B. Participants in Part A, the Blinded Phase of this study are blinded to their treatment assignment. Given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met per the protocol-defined interim analysis, Part B, the Open-Label Observational Phase of this study is designed to offer participants who received placebo in Part A of this study and who meet Emergency Use Authorization (EUA) eligibility, an option to request open-label mRNA-1273 (Figure 1).

4.1.1. Part A, the Blinded Phase

The Blinded Phase of this study is a randomized, stratified, observer-blind, placebo-controlled evaluation of the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The study schematic is presented in Figure 1.

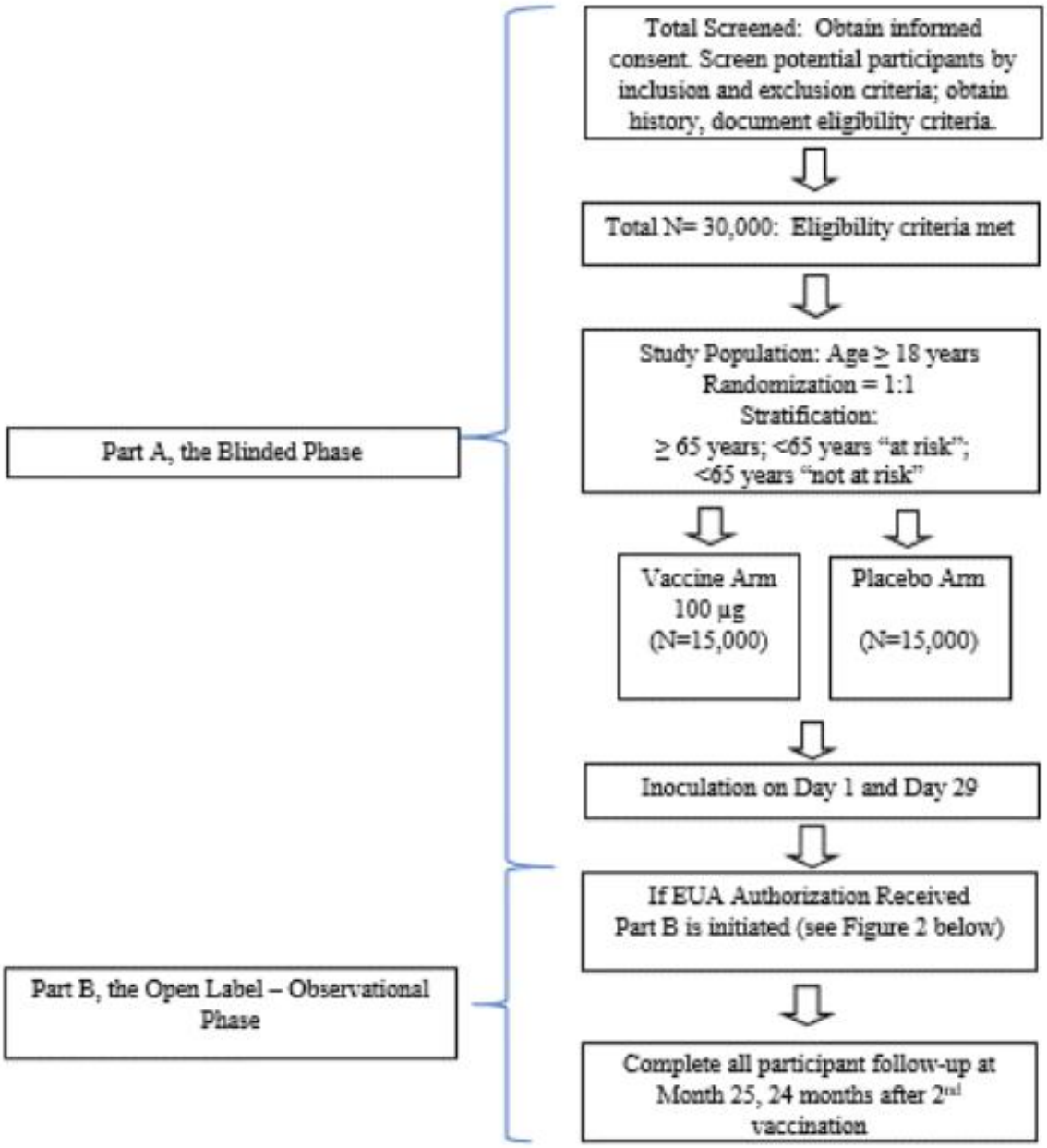
Approximately 30,000 participants will be randomly assigned to receive either 100 µg of mRNA-1273 vaccine or a placebo control in a 1:1 randomization ratio. Assignment will be

stratified by age and health risk. This is a case-driven study and thus final study size will depend on the actual attack rate of COVID-19.

The study duration will be approximately 26 months for each participant, including a screening period of up to 1 month and a study period of 25 months that consists of 2 IP injections and 24 months afterward. Participants are considered to have completed the study if they complete the final visit at Day 759 (Month 25), 24 months following the last injection of IP. All participants will be assessed for efficacy and safety endpoints and provide a NP swab sample and blood sample before the first and second injection of IP in addition to a series of post-dose blood samples for immunogenicity through 24 months after the second injection of IP. Efficacy assessments will include surveillance for COVID-19 with RT-PCR confirmation of SARS-CoV-2 infection after the first injection of IP.

Participants will use an electronic diary (eDiary) to report solicited adverse reactions (ARs) after each injection of IP and to prompt an unscheduled clinic visit if experiencing any symptoms of COVID-19. Surveillance for COVID-19 will be performed through weekly contacts with the participants via a combination of telephone calls and completion of an eDiary starting at Day 1 through the end of the study. An illness visit will be scheduled if the participant is experiencing COVID-19 symptoms.

Figure 1: **Study Flow Diagram: Part A, the Blinded Phase followed by Part B, the Open-Label Observational Phase**



4.2. Statistical Hypothesis

For the primary efficacy objective, the null hypothesis of this study is the VE of mRNA-1273 to prevent first occurrence of COVID-19 is ≤ 30%, i.e. $H_0^{efficacy}$: VE ≤ 0.3.

The study will be considered meeting the primary efficacy objective if the confidence interval (CI) of VE rules out 30% at either one of the interim analyses or at the primary analysis.

4.3. Sample Size and Power

The sample size is driven by the total number of cases to demonstrate the VE (mRNA-1273 vs. placebo) to prevent COVID-19. Under the assumption of proportional hazards over time and with 1:1 randomization to vaccine: placebo, a total of 151 COVID-19 events will provide 90% power to detect a 60% reduction in hazard rate, rejecting the null hypothesis H_0: VE ≤ 30%, with 2 interim analyses at 35% and 70% of the total events using a 1-sided O'Brien-Fleming boundary for efficacy and a log-rank test statistic with a 1-sided false positive error rate of 0.025. The total number of cases pertains to the Per-Protocol (PP) population, starting 14 days after the second injection of IP (refer to the protocol Section 9.3). Under the specified assumptions, up to approximately 30,000 participants will be randomized. It will take approximately 5, 8, and 10 months from study start (first subject first dose), respectively, to accrue 35% (approximately 53), 70% (approximately 106) and 100% (151) of the target number of cases in the PP Set.

For the secondary objective on the VE against serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomology or severity (COV-INF), the study will have ≥ 90% power to demonstrate the VE is above 30% (to reject null hypothesis VE ≤ 30%) at 1-sided alpha of 2.5% if the true VE to prevent COV-INF is 60%, because every COVID-19 disease endpoint is necessarily a COV-INF endpoint. For the secondary objective on the VE against severe COVID-19, the power depends on the number of severe COVID-19 cases (Table 7 in the protocol).

4.4. Randomization

Approximately 30,000 participants will be randomly assigned in 1:1 ratio to receive either mRNA-1273 100 µg or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT) at the Day 1 visit, in accordance with pre-generated randomization schedules. Participants will be stratified by age (≥ 18 and < 65, or ≥ 65 years) and, if they are < 65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 based on recommendation by the US Centers for Disease Control and Prevention (CDC) as of March 2020. There will be 3 strata for randomization:

- ≥ 18 and < 65 years and not at risk
- ≥ 18 and < 65 years and at risk
- ≥ 65 years

At least 25% of enrolled participants, but not to exceed 50%, will be from the ≥ 65 years age group and < 65 years at risk group.

4.5. Blinding and Unblinding

This study is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with the certain exceptions specified in Section 6.2.8 of the protocol.

The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Planned interim and primary analyses are described in Section 6.4.1 of this SAP and Section 9.6 of the protocol. Participant-level unblinding will be restricted to an independent unblinded statistician and, as needed, statistical programmer(s) performing the IAs, who will have no other responsibilities associated with the study.

In addition to the routine study monitoring outlined in this protocol, an external DSMB will review interim data to safeguard the interests of clinical study participants and to enhancing the integrity of the study. The DSMB will review treatment-level results of the IAs, provided by the independent unblinded statistician. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IAs, if required, in order to act on the recommendations of the DSMB. The extent to which individuals are unblinded with respect to results of IAs will be documented. Depending on the recommendation of the DSMB, the Sponsor may prepare a regulatory submission after an IA. In this case, pre-identified Sponsor members including the analysis and reporting team will be unblinded to treatment assignments and remain unblinded for the remainder of the study. The limited Sponsor and CRO team members to be unblinded in this case will be pre-specified in the study Data Blinding Plan. Participants and investigators will remain blinded until the unblinding or participant decision visit.

5. Analysis Populations

The following analysis sets are defined: Randomization Set, Full Analysis Set, Modified Intent-to-Treat, Per-protocol Set, Immunogenicity Subset, Solicited Safety Set, and Safety Set.

5.1. Randomization Set

The Randomization Set consists of all subjects who are randomized, 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) consists of all randomized participants who received at least one dose of IP. Participants will be analyzed according to the treatment group to which they were randomized.

5.3. Modified Intent-to-Treat Set

The Modified Intent-to-Treat (mITT) Set consists of all participants in FAS who had no immunologic or virologic evidence of prior COVID-19 (ie, negative NP swab test and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP, i.e. all FAS participants excluding those with PCR and/or serology positive at baseline (Day 1 before the first dose of IP).

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

5.4. Per-Protocol Set

The Per-protocol Set consists of all participants in mITT who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to database lock (DBL) and unblinding, which impact critical or key study data. Participants will be analyzed according to the treatment group to which they were randomized. Participants who did not receive the second injection of IP within [21, 42] days after the first injection date will be excluded from the Per-Protocol Set.

5.5. Immunogenicity Subset and Analysis Populations for Immunogenicity

For characterizing immunogenicity of the vaccine, and for assessing correlates of risk and protection, a case-cohort sampling design will be used for measuring bAb and nAb data from a randomly sampled subset of trial participants [the case-cohort Immunogenicity Analysis Set (ccIAS)], or Immunogenicity SubSet. The ccIAS cohort consists of a stratified random sample of trial participants (Random SubCohort), augmented with a subset or all primary endpoint cases and SARS-CoV-2 infection endpoint cases. The immunogenicity samples of the ccIAS cohort will be processed and the immunogenicity data will be available for the ccIAS cohort. The Immunogenicity Subset consists of all

participants in the ccIAS who had a valid baseline immunogenicity test result (prior to the first injection of IP) and at least one valid post-baseline result.

The analysis of characterizing immunogenicity of mRNA-1273 is included in Section 6.7 of this SAP, the primary analysis population to characterize immunogenicity of mRNA-1273 is the Per-Protocol Random Subcohort for Immunogenicity (Section 6.7.2); the analysis of assessing correlates of risk and protection will be included in a separate Immune Correlates SAP. Details of the case-cohort sampling, and analysis populations for characterizing immunogenicity of mRNA-1273 are also included in Section 6.7 of this SAP.

5.6. Solicited Safety Set

The Solicited Safety Set consists of randomized participants who received at least one dose of IP and contributed any solicited AR data, i.e. have at least one post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment group corresponding to the study vaccination they actually received.

In addition, the following Solicited Safety Set is defined for each injection separately. The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days.

Participants will be analyzed according to the treatment group a subject received, rather than the vaccination group to which the participant was randomized. If a participant was randomized to placebo but received any dose of mRNA-1273 vaccine at any injection, the participants will be included in the mRNA-1273 group in the Solicited Safety Set.

5.7. Safety Set

The Safety Set consists of all randomized participants who received at least one dose of IP. The Safety Set will be used for all analysis of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the IP they actually received. For a participant who was randomized to placebo but received any dose of mRNA-1273 at any injection, the participant will be included in the mRNA-1273 group in the Safety Set.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Events is provided in the protocol Table 16-19.

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 IP.

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 baseline SARS-CoV-2 serostatus and treatment group within the analysis set of interest, unless otherwise specified.

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 (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) 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 (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at Day 1.

The baseline SARS-CoV-2 status is defined as missing for subjects with both tests missing, or with one test missing and one test negative.

Subjects with negative Baseline SARS-CoV-2 status will be included in the mITT population; subjects with positive or missing baseline SARS-CoV-2 status will be excluded from the mITT and PP population.

Age: unless otherwise specified, age is calculated as the age at screening. In subgroup analyses on age, age at screening will be used for derivation of age group.

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 it is prior to the second injection, then study day is calculated as b); If it is after the 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.

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 measurements.
- In the derivation of maximum/minimum values after 1st dose 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 dates of prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- If the laboratory results are reported as below the LLOQ (e.g. < 0.1), the numeric values will be substituted by 0.5 × LLOQ in the summary when treating the results as continuous variables. If the laboratory results are reported as greater than the ULOQ (e.g. > 3000), the numeric values will be substituted by ULOQ in the summary statistics for continuous variable.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups

The following treatment groups will be used for summary purposes in Part A:

- mRNA-1273
- Placebo

If a subject received any dose of mRNA-1273 at any injection, regardless of the treatment group the subject was randomized to, the subject will be included to mRNA-1273 100 μg group as the actual treatment group received for safety analyses.

All analyses and data summaries/displays for disposition, baseline demographics and characteristics will be provided by Baseline SARS-CoV-2 Status (negative, positive, and overall) and treatment group unless otherwise specified. All analyses and data summaries/display for efficacy will be provided by treatment group using appropriate analysis population unless otherwise specified.

Analysis Periods

The following analysis periods and treatment groups will be used for efficacy analyses for the blinded phase (Part A):

Part A Group	Description	Blinded/Part A Analysis Period for Efficacy
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase	From randomization to earlier date of Participant Decision Visit (PDV)/unblinding, study discontinuation, study completion, death, or data cutoff date for efficacy)
Placebo	Participants randomized to Placebo in the Blinded Phase	

The analysis period and treatment groups of the blinded phase (Part A) for Safety analyses is summarized below:

Part A Group	Description	Blinded/Part A Analysis Period for Safety

mRNA-1273	Participants received at least one dose of mRNA-1273 in the Blinded Phase	From the first dose of study IP to the earlier date of (study discontinuation, study completion, death, data cutoff for safety, PDV/unblinding) for those who did not receive study IP in Part B. For participants received study IP in Part B, from the first dose of study IP in study to the earlier date of (data cutoff for safety, or 1st dose of study IP in Part B)
Placebo	Participants only received Placebo in the Blinded Phase	

The above analysis period for safety analysis in Part A is also referred to as Overall Period in Part A. For Part A, up to 28 days after any vaccination, 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]), will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

Part B

Considering Part B/unblinded phase of the study, the following analysis periods may be used. SAP Part B will provide more details, and if the definition for Part B in SAP Part B differs from that described in this SAP, SAP Part B will prevail.

The following analysis period and treatment groups for Efficacy of the unblinded phase (Part B) may be used:

Part B Cohort	**Description**	**Part B Analysis Period for Efficacy**
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase	From PDV/unblinding to earlier date (data cutoff date for efficacy, last observed in Study) where last observed is earlier of (study discontinuation, study completion, death)
Placebo	Participants randomized to Placebo in the Blinded Phase and did not receive mRNA-1273 in Part B	
Placebo-mRNA-1273	Participants randomized to Placebo in the Blinded phase and received mRNA-1273 in Part B	

The following analysis period of the unblinded phase (Part B) and treatment groups for Safety analysis of the unblinded phase (Part B) may be used:

Part B Cohort	Description	Part B Analysis Period for Safety
mRNA-1273	Participants received at least one dose of mRNA-1273 in the Blinded Phase	From PDV/unblinding to earlier date of (data cutoff date for safety, last observed in Study). If a participant received mRNA-1273 in Part B, from 1st date of study IP in Part B to earlier date of (data cutoff date for safety, last observed in Study).
Placebo	Participants only received Placebo in the Blinded Phase and did not receive mRNA-1273 in Part B	From PDV/unblinding to earlier date of (data cutoff date for safety, last observed in Study)
Placebo-mRNA-1273	Participants only received Placebo in the Blinded phase and received mRNA-1273 in Part B	From first dose of mRNA-1273 in Part B to earlier date of (data cutoff date for safety, last observed in Study)

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

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories (analysis sets defined in Section 5) will be summarized as defined in Section 6.1 based on Randomization Set:

- Randomization Set
- Full Analysis Set
- Modified Intent-to-Treat Set
- Per-protocol Set
- Solicited Safety Set
- Safety Set

The denominators of the percentages will be based on subjects in the Randomization Set. 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 randomized subjects will be summarized by site and by stratification factor at randomization (i.e. ≥ 18 and < 65 years and not at risk, ≥ 18 and < 65 years and at risk, or ≥ 65 years) separately based on the Randomization Set.

The number and percentage of subjects in each of the following disposition categories will be summarized based on the Randomization Set:

- 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

Subjects with any inclusion and exclusion criteria violation will be provided in a listing.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2)). The number and percentage of subjects will be provided for categorical variables such as age group, sex, race, ethnicity, randomization stratum under which the subject was randomized, and risk factors at Screening (have at least one of the following):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m^2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection

The summaries will be provided separately based on the FAS, Safety Set, mITT Set and PP Set.

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 mRNA-1273 and then alphabetically within SOC.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccinations will be coded using the 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 Appendix C Table 11 and will be summarized.

The number and percentage of subjects who continued or newly received concomitant medications and non-study vaccinations will be summarized by treatment group by PT in descending frequency in the mRNA-1273 group:

- Any concomitant medications
- Any non-study vaccine
- Antipyretics or analgesics medication, summaries will be provided for during the 7-day follow-up period of each injection, and during the 28 days follow-up period after each injection (for 1st injection, up to 2nd injection or 28 days after the 1st injection)

6.2.5. Study Exposure

Number and percentage of subjects receiving 1st and 2nd injections will be summarized by treatment arm, the timing of the 2nd injection will be summarized by arm.

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 treatment group as defined in Section 6.1 based on the Randomization Set.

Select major protocol deviations impact critical or key study data, and subjects with such deviations will be excluded from the Per-Protocol Set for efficacy analyses, such major protocol deviations will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from Per-Protocol Set for efficacy will be summarized.

6.3. Efficacy Analysis

The PP Set is the primary analysis population for efficacy analyses, unless otherwise specified. PP Set, mITT Set, and FAS will be used for efficacy analyses and subjects will be included in the treatment group which they are randomized to.

Surveillance for COVID-19 will be performed starting after enrollment through the end of the study.

An Adjudication Committee (AC) blinded to treatment assignment will review potential cases and adjudicate COVID-19, the primary efficacy endpoint, and severe COVID-19. Adjudication committee assessments have been used in the two efficacy analyses that have been performed to date: the first interim analysis based on data snapshot occurred on 11-Nov-2020, the primary analysis based on data snapshot occurred on 25-Nov (please refer to Section 6.4.2). Adjudication committee assessments will be used in the final efficacy analysis of the blinded data (Section 6.4.3).

Baseline SARS-CoV-2 status is described in Section 6.1. Baseline SARS-CoV-2 status, RT-PCR test results at baseline, serology status at baseline (bAb specific to SARS-CoV-2 nucleocapsid [NP], as measured by Roche Elecsys Anti-SARS-CoV-2 assay) will be summarized by treatment group.

The mITT and PP Sets will only include participants with baseline negative SARS-CoV-2 status.

RT-PCR test results, and bAb specific to SARS-CoV-2 NP will be summarized by visit.

6.3.1. Analysis of the Primary Efficacy Endpoint

6.3.1.1. Primary Efficacy Endpoint Definition/Derivation

The primary efficacy objective is the VE of mRNA-1273 to prevent occurrence of COVID-19 starting 14 days after the second dose of IP. COVID-19 is defined as symptomatic disease based on the criteria specified in Section 8.1.1 of the protocol. Cases

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

Subjects reporting COVID-19 symptoms, as defined in Section 8.1.2 of the protocol, will be asked to use an eDiary to report COVID-19 symptoms, and an Illness Visit will be scheduled to collect an NP swab if COVID-19 symptoms are reported (refer to Section 8.1.2 of the protocol).

For the primary efficacy endpoint, a COVID-19 case will be identified as a positive post-baseline RT-PCR test result that is prompted by symptom(s), together with eligible symptoms, i.e. a positive PCR result of the eligible symptoms summarized below in Table 1.

An independent Adjudication Committee (AC) blinded to treatment assignments will review potential cases and adjudicate COVID19 and severe COVID-19 events and the date of COVID-19 and severe COVID-19.

Two sets of COVID-19 will be provided:

- Based on Adjudication Committee assessments
- Based on eligible COVID-19 symptoms (at least 2 systemic symptoms or 1 respiratory symptom) and positive RT-PCR.

Table 1: Derivation for COVID-19 (primary efficacy endpoint)

	COVID-19
Post-baseline PCR results at illness visits prompted by symptom(s)	Positive, **AND**
Systemic Symptoms	at least **TWO** of the following **systemic symptoms**: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); **OR**

Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia;

The date of documented COVID-19 (case) will be the later date of ([2 eligible systemic symptoms reported, or 1 eligible respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented 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 2nd eligible systemic symptom is reported

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

Time to the 1st occurrence of COVID-19 = Date of documented COVID-19 – Date of randomization +1.

In the primary analysis approach for the primary efficacy endpoint, cases will be counted starting 14 days after the 2nd injection, i.e. date of documented COVID-19 – Date of the 2nd injection $\geqslant$ 14 (starting 14 days after the 2nd injection).

In the primary analysis approach for the primary efficacy endpoint, the first occurrence of COVID-19 starting 14 days after the 2nd injection will be considered event. In the various sensitivity analyses planned to examine the onset of COVID-19, the censoring rules of cases are outlined in Table 2 below.

In this study, during the blinded phase, there is a scheduled NP swab test at the Day 29 visit prior to the 2nd injection of IP; and blood samples are collected with bAb against SARS-CoV-2 nucleocapsid (NP) tested at months 1, 2, 7, 13 and 25. At IA1 and the Primary Analysis of efficacy, RT-PCR results at scheduled pre-dose 2 (Day 29) and bAb against SARS-CoV-2 nucleocapsid at Day 29 were not considered in the derivation of COVID-19.

At the final blinded efficacy analysis, subjects with early infection, as detected by positive RT-PCR at scheduled pre-dose 2 visit (Day 29), or positive bAb against SARS-CoV-2 NP in blood samples at the scheduled visits, are censored at the time of early infection. If a participant had eligible symptom(s) within 14 days of positive RT-PCR at scheduled pre-dose 2 visit, the participant is considered to be a case for COVID-19.

6.3.1.2. Primary Analysis Approach

The number and percentage of subjects who had an event (i.e. the first occurrence of COVID-19 starting 14 days after the second injection, date of documented COVID-19 – date of the second injection ≥ 14) and subjects who were censored will be summarized.

The non-parametric Kaplan-Meier method will be used to estimate the time to first occurrence of COVID-19 curve in each treatment group.
Vaccine efficacy (VE) is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1273 vs. placebo), i.e. one minus the hazard ratio (HR). The null hypothesis is:

$$H_0^{efficacy}: \text{vaccine efficacy} \leq 0.3$$

Equivalently, the null hypothesis is:

$$H_0^{efficacy}: \text{hazard ratio (HR)} \geq 0.7$$

A stratified Cox proportional hazard (PH) model with Efron's method of tie handling and with treatment group as covariate will be used to assess the magnitude of the treatment group difference (i.e. HR) between mRNA-1273 vs. placebo. The same stratification

factors used for randomization (Section 4.4) will be applied to the stratified Cox model. VE with corresponding alpha-adjusted confidence interval (CI), 95% CI, and one-sided *p*-value for testing the null hypothesis from the stratified Cox model would be reported at a planned interim analysis up to the analysis at which vaccine efficacy is demonstrated. After vaccine efficacy was demonstrated, VE and 95% CI would be provided for subsequent analysis/updates of efficacy.

In this study, vaccine efficacy was demonstrated based on pre-specified statistical criterion (Section 6.4) at the first interim analysis, at which, one-sided p-value for testing the null hypothesis of VE≤ 0.3, 95% CI and alpha-adjusted CI were provided from the stratified Cox model. At the primary analysis where the total number of COVID-19 cases > 151, total target number of cases, VE, one-sided p-value for testing the null hypothesis of VE≤ 0.3 and 95% CI were provided. In subsequent analysis/updates of efficacy, VE and 95% CI will be provided.

For the primary analysis, subjects who have no documented COVID-19 will be censored at the last study assessment date. Subjects who discontinue the study early or die due to causes unrelated to COVID-19 without documented COVID-19 will be censored at the date of early discontinuation or death. Subjects who experience an early COVID-19 up to 14 days after the second injection of IP will be censored at the time of documented COVID-19.

As in PP Set definition, subjects who missed study IP administration, who were seropositive at baseline, or who had major protocol deviations that impact critical or key data, will be excluded from the PP Set.

The number and percentage of subjects who had an event (i.e. the first occurrence of COVID-19 at least 14 days after the second injection) will be reported.

Potential intercurrent events to the estimand are listed in Appendix F Table 9. The primary estimand with rationale for strategies to address intercurrent events is summarized in Appendix F 10.

6.3.1.3. Sensitivity Analyses with COVID-19 Cases Counted Starting at Various Timepoints

Sensitivity analyses will be performed with COVID-19 cases counted starting at various timepoints as below using the PP Set. The censoring rules for analyses of the primary endpoint are summarized in Table 2.

- immediately after the second injection of IP
- 14 days after the first injection of IP (also as primary analysis approach for the secondary efficacy objective: To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP.)
- immediately after the first injection of IP
- immediately after randomization

If <10% of the COVID-19 cases received the first injection after the day the subject was randomized, sensitivity analysis with COVID-19 cases counted starting after the first injection of IP may not be performed separately, as it would be very similar to the sensitivity analysis with COVID-19 cases counted starting from randomization.

Table 2: Censoring Rules for COVID-19

Situation	**Primary Efficacy Approach (cases ≥14 days after Dose 2)**	**Sensitivity Analyses**			
		Cases starting after Dose 2	**Cases ≥14 days after Dose 1**	**Cases starting after Dose 1***	**Cases starting after randomization**
Early case from randomization up to first injection	Censored at date of case	Censored at date of case	Censored at date of case	Censored at date of case	Event
Early case from Dose 1 up to (<) 14 days after Dose 1	Censored at date of case	Censored at date of case	Censored at date of case	Event	Event
Early case from ≥14 days after Dose 1 up to (<) Dose 2	Censored at date of case	Censored at date of case	Event	Event	Event
Early case from Dose 2 up to (<)14 days after Dose 2	Censored at date of case	Event	Event	Event	Event
Case ≥14 days after Dose 2	Event	Event	Event	Event	Event
Early discontinuation or death without documentation of COVID-19	Censored at date of discontinuation/death				

Situation	Primary Efficacy Approach (cases ≥14 days after Dose 2)	Sensitivity Analyses			
		Cases starting after Dose 2	Cases ≥14 days after Dose 1	Cases starting after Dose 1*	Cases starting after randomization
Early infection as detected by: positive RT-PCR at scheduled visit (pre-dose 2), or, positive bAb against SARS-CoV-2 NP in blood samples at the scheduled visits	Censored at date of early infection				

* To be performed if there are ≥ 10% of total cases with Dose 1 date > randomization date

Analysis of the primary efficacy endpoint based on the mITT Set will also be performed using the same statistical methods used for the primary analysis. The above sensitivity analyses will be also performed with COVID-19 cases counted starting at various timepoints using the mITT Set.

6.3.1.4. Subgroup Analysis

To assess consistency of VE across various subgroups, subgroup analyses of the primary efficacy endpoint will be performed in select subgroups specified below based on the PP Set. The primary efficacy endpoint will be analysed by each of the subgroups using the same methods described for the primary analysis, i.e. the stratified Cox proportional hazard model with Efron's method of tie handling with a single treatment covariate, and the estimate of VE and its 95% CI will be provided within each category of the following classification variables:

- Age groups: ≥ 18 and < 65 years, ≥ 65 years
- Age groups: ≥ 18 and < 65 years, ≥ 65 years and < 75 years, and, ≥ 75 years
- Stratification factor at randomization: ≥ 18 and < 65 years and not at risk, ≥ 18 and < 65 years at risk, ≥ 65 years
- Sex (female, male)
- Race
- Ethnicity
- Race and Ethnicity: non-Hispanic white, communities of color
- Each risk factor for severe COVID-19 illness as listed in Section 6.2.1 of the protocol

If the number of subjects in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses. Forest plots will be provided for VE and its 95% CI for the subgroup analyses based on PP Set. Subgroup analyses based on the mITT Set may be performed.

Recently, new SARS-CoV-2 variants have emerged. COVID-19 cases may be sequenced and depending on the findings, summary of cases genotypically distinct and genotypically similar to vaccine by treatment assignment may be provided. Analysis of vaccine efficacy against variants may be performed if there are sufficient numbers of variants cases.

6.3.1.5. Supportive Analysis Using Exact Method Based on Incidence Rate

Incidence rate will be provided for each treatment group. Incidence rate will be calculated as the number of subjects with an event (i.e. first occurrence of COVID-19 at least 14 days after the second injection) divided by the number of subjects at risk adjusted by person-time (years) in each treatment group. The person-time is calculated as the time from randomization to the date of the first event for subjects with an event, and the time from randomization to the date of censoring for subjects without an event (or who are censored). Person-time, incidence rate, and 95% CI for incidence rate will be provided by treatment group.

As a supportive analysis, VE will also be estimated by one minus the ratio of incidence rate (mRNA-1273 vs. placebo), i.e. 1- ratio of incidence rate (mRNA-1273 vs. placebo) adjusting for person-time, and the 95% CI of VE will be computed using the exact method conditional upon the total number of cases adjusting for person-time.

6.3.2. Analysis of the Secondary Efficacy Endpoints

A sequential/hierarchical testing procedure will be used to control type 1 error rate over the primary efficacy endpoint and the secondary efficacy endpoints. Secondary efficacy endpoints will only be tested when the primary efficacy endpoint achieves statistical significance. Multiplicity adjustments among the secondary efficacy endpoints may be performed for secondary efficacy endpoints as described in Section 6.5.

6.3.2.1.Derivation of Secondary Efficacy Endpoint: Severe COVID-19

Derivation of select secondary efficacy endpoints are included in this section.

6.3.2.1.1. Derivation of Secondary Efficacy Endpoint: Severe COVID-19

Severe COVID-19 is defined as:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, AND
- any of the conditions listed in Section 3.2.1 (Section 8.1.1 of the protocol).

The date of documented severe COVID-19 will be the later date of:

- Date of documented COVID-19,
- Date of eligible symptom for severe COVID-19, defined as the earliest of the first eligible severe symptom is reported

The date of eligible symptoms for severe COVID-19 should be within 28 days after the positive RT-PCR result used in the confirmation of COVID-19.

The time to the first occurrence of severe COVID-19 will be calculated as:

Time to the 1st occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of randomization +1

The independent AC blinded to treatment assignments will adjudicate severe COVID-19 events. Two sets of severe COVID-19 will be provided:

- Based on Adjudication Committee assessments
- Based on eligible symptoms for severe COVID-19, and positive RT-PCR.

6.3.2.1.2. Derivation of a secondary definition of COVID-19

A secondary definition of COVID-19 is defined as any of the listed systemic symptom in Section 8.1.1 of the protocol AND with a positive RT-PCR test.

Date of the documented secondary definition of COVID-19 will be later date of:

- Date of the positive RT-PCR test (prompt by symptom)
- Date of eligible symptom for secondary definition of COVID-19, defined as the earliest date of first eligible symptom is reported

and the two dates should be within 14 days of each other.

The same censoring rule as summarized in Table 2 for the primary definition of COVID-19 will be used for the secondary definition of COVID-19 and corresponding sensitivity analyses with cases starting at different timepoint.

6.3.2.1.3. Derivation of serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity

For the secondary efficacy endpoint: serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity [COV-INF], any post-baseline positive RT-PCR results will be considered, including those from the scheduled NP swab tests at Day 29 visit prior to the 2nd injection of IP as well as the those prompted by symptom(s). In addition, seroconversion due to infection will also be considered.

The analysis population for COV-INF will be the Per-Protocol Set and the mITT Set that include participants with negative SARS-CoV-2 status at baseline. Seroconversion due to infection is defined for participants with negative SARS-CoV-2 status at baseline as becoming seropositive (positive bAb specific to SARS-CoV-2 NP) as measured by *Roche Elecsys* on study (at scheduled visits post baseline). A COVID-19 case or secondary definition of COVID-19 case will always be an INF case.

The date of documented infection regardless of symptom [COV-INF] will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of seroconversion due to infection

In the primary approach, documented infection is counted starting 14 days after the 2nd dose, which requires a positive RT-PCR result starting 14 days after the 2nd IP dose, or seroconversion at Day 57 visit or later.

Derivation of this secondary efficacy endpoint is summarized in Table 3.

Table 3: Derivation of Secondary efficacy endpoint: Serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity – mITT Set or Per-Protocol Set

Baseline SARS-CoV-2 Status	Post-baseline assessments		**Secondary endpoint**: serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity
	PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	
Negative at Baseline	**positive** (either at symptom-prompt NP swab test [Illness visit], or at scheduled NP swab test)		Case
Negative at Baseline		Seroconversion (positive on study at scheduled visits) as measured by *Roche Elecsys*	Case

6.3.2.1.4. Derivation of asymptomatic SARS-CoV-2 infection

Asymptomatic SARS-CoV-2 infection will be analyzed using the Per-Protocol Set and mITT Set. Asymptomatic infection is identified by absence of symptoms and infections as detected by RT-PCR or seroconversion. Specifically:

- Absent of symptoms (no COVID-19 symptom for either primary efficacy endpoint of COVID-19, or secondary definition of COVID-19),
- AND at least one from below:
    - seroconversion (bAb specific to SARS-CoV-2 nucleocapsid) at scheduled visits (months 1, 2, 7, 13 and 25 if applicable in Part A, Participant Decision Visit and etc. in Part B), when blood samples for immunogenicity are collected, or
    - by RT-PCR at scheduled visits such as pre-dose 2 at Day 29 in Part A, both RT-PCR test and bAb against SARS-CoV-2 nucleocapsid will be considered.

The date of documented asymptomatic infection is the earlier date of seroconversion due to infection, or positive RT-PCR at scheduled visits, with absence of symptoms. Participants who had a symptomatic infection (COVID-19 or secondary definition of COVID-19) prior to an asymptomatic infection will be censored at the time of symptomatic infection for the analysis of asymptomatic infection. In the primary approach, documented asymptomatic infection is counted starting 14 days after the 2nd IP dose, which requires seroconversion at months 2 (Day 57 visit) or later.

6.3.2.2. Analysis of the secondary efficacy endpoints

Similar analysis methods as for the primary efficacy endpoint will be applied to the following secondary efficacy endpoints based on the PP set, unless otherwise specified:

- VE to prevent severe COVID-19
- VE to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.

- VE to prevent COVID-19 using a secondary definition of symptoms
- VE to prevent death caused by COVID-19

For each of the above secondary objectives, the following analyses will be performed:

- Primary analysis: VE will be estimated with 1 - HR (mRNA-1273 vs. placebo) using a Cox PH model based on the PP Set as described for the primary efficacy endpoint. Kaplan-Meier curves of time to event will be presented for each treatment group.

  Cases will be counted starting 14 days after the second injection of IP.

- Analysis using the same model based on the mITT Set as described for the primary efficacy endpoint. Kaplan-Meier curves of time to event will be presented for each treatment group.
- Sensitivity analyses with cases counted starting immediately after the second injection of IP (onset date >= date of dose 2, considering positive RT-PCR at Day 29), starting 14 days (>= 14 days) after the first injection of IP, and immediately after randomization respectively.
- VE and 95% CI based on the incidence will be estimated with 1 - ratio of incidence rates using the exact method conditional upon the total number of cases.

<u>For the secondary efficacy objective: VE to prevent asymptomatic SARS-CoV-2 infection</u>

As diseased cases (COVID-19 or secondary definition of COVID-19) are competing events for asymptomatic SARS-CoV-2 infections, competing risk method will be used to estimate the vaccine efficacy of mRNA-1273, specifically, Fine and Gray's (FG) sub-distribution hazard model will be used. Competing risk method will also be used to estimate the cumulative incidence function and the cumulative incidence of asymptomatic SARS-CoV-2 infections will be plotted.

In the primary approach with cases of asymptomatic SARS-CoV-2 infection counted starting 14 days after the second injection, only seroconversion at Day 57 or later will be considered.

As serum samples were taken at scheduled visits (e.g. Day 29[month 1], Day 57[month 2]), sensitivity analyses with cases counted starting after 2nd dose, 14 days after first dose, after first dose and after randomization are the same. Only one set of sensitivity analysis with cases counted starting from randomization will be provided. In this sensitivity analysis, asymptomatic cases detected by positive RT-PCR result at scheduled pre-dose 2 visit (Day 29), or seroconversion at timepoints with scheduled visits will be considered. Sensitivity analysis using the mITT Set with cases counted starting from 14 days after the second injection, and from randomization will also be performed.

Stratified Cox PH model may also be used.

For the secondary efficacy objective: VE to prevent COVID-19 after the first injection of IP

This endpoint will be analyzed as a sensitivity analysis of the primary efficacy endpoint with cases counted starting 14 days (>=14 days) after the first injection of IP as described in Section 6.3.1.

For the secondary efficacy objective: VE to prevent COVID-19 disease regardless of prior SARS-CoV-2 infection

This endpoint will be analyzed using the FAS. The same methods described above for the primary efficacy endpoint will be applied with cases counted starting 14 days after the second injection of IP.

Sensitivity analyses with cases counted starting immediately after the second injection, 14 days after the first injection, and after randomization will also be performed. In sensitivity analysis with cases counted starting after the second

injection, subjects who received only the first injection and is a case will be censored at the time of COVID-19.

The VE will also be estimated with 1- ratio of incidence rates with the 95% CI using the exact method conditional upon the total number of cases adjusting for person-time.

In addition, an exploratory analysis with the same Cox model will be carried out in the subgroup of FAS whose baseline SARS-CoV-2 status is positive with cases counted starting from randomization to assess the VE in those with positive baseline SARS-CoV-2 status, at baseline, if sample size permits. Such analysis in the subgroup of FAS whose baseline SARS-CoV-2 status is negative with cases counted starting from randomization is the same as the sensitivity analysis of COVID-19 starting from randomization in mITT.

6.4. Planned Analyses and Analyses of Efficacy Analyses that Have Been Conducted

6.4.1. Planned Interim Analyses and Primary Analysis

There were two planned interim analyses in this study, which would be performed when approximately 35% and 70% of the target total number of COVID-19 cases across the two vaccine groups had been observed respectively. The primary objective of the IAs was for early detection of reliable evidence that VE is above 30%. The Lan-DeMets O'Brien-Fleming approximation spending function was used for calculating efficacy bounds and to preserve the (1-sided) 0.025 false positive error rate over the two IAs and the primary analysis (when the target number of cases have been observed), relative to the null hypothesis ($H_0^{efficacy}$: VE $\leq$ 30%). There is no intention to stop the study early if the efficacy had been demonstrated at any of the IAs. If efficacy was demonstrated at an IA, the subsequent IA or primary analyses would be considered supportive in nature. The IA results would be reviewed by the DSMB.

The first IA would occur when 35% of the total cases in the PP set had been observed. The study would be considered positive at this IA if the one-sided *p*-value for rejecting VE $\leq$

30% (HR ≥ 0.7) was less than 0.0002 based on the Lan-DeMets O'Brien-Fleming approximation spending function. This corresponds to an observed HR of approximately 0.259, or an observed VE approximately 0.741.

The second IA would occur when 70% of the total cases have been observed in the PP set. The study will be considered positive at this IA if the *p*-value for rejecting VE ≤ 30% (HR ≥ 0.7) was less than 0.0073 based on the Lan-DeMets O'Brien-Fleming approximation spending function. This corresponds to an observed HR of approximately 0.435, or an observed VE of approximately 0.565.

The primary analysis would be performed when approximately 151 cases have been observed in the PP Set. The study would be considered positive at the primary analysis when a total of 151 cases had been observed and if the one-sided *p*-value for rejecting HR ≥ 0.7 was less than 0.0227. This corresponds to an observed hazard ratio of approximately 0.505 or observed VE of approximately 0.495.

An independent, unblinded statistics team would carry out the IAs. The unblinded statistics team would not be involved in either study design or the regular study conduct. The subjects and study sites will remain blinded throughout the study.

The final analysis would be performed after all subjects have completed the study and after the database is cleaned and locked. Results of this analysis would be presented in a CSR.

The timing, number of cases and decision guidance at each IA and primary analysis is summarized in the table below (Table 13 of the protocol).

Table 4: Interim Boundaries Using O'Brien-Fleming Spending function, Calculation Based on the PP Set for the Primary Efficacy Endpoint

Information fraction (% of total #cases)	Number of cases	Nominal Alpha	Efficacy Boundary Rejecting H0: VE ≤ 30% (HR ≥ 0.7)	Cum Prob (crossing efficacy boundary if the true VE = 60%)
IA1 35%	53	0.0002	VE ≥ 0.741 (HR ≤ 0.259)	4.6%
IA2 70%	106	0.0073	VE ≥ 0.565 (HR ≤ 0.435)	61.5%
Primary analysis 100%	151	0.0227	VE ≥ 0.495 (HR ≤ 0.505)	90.0%

Abbreviations: HR = hazard ratio; IA: interim analysis; PP = per-protocol; VE = vaccine efficacy.

6.4.2. Analyses of Efficacy that Have been Conducted

Two efficacy analyses have been performed in this study as of this SAP amendment.

6.4.2.1.The First Interim Analysis

The primary efficacy endpoint of mRNA-1273-P301 is COVID-19, defined as the first occurrence of COVID-19 starting 14 days after the 2nd injection.

For the primary efficacy objective, the null hypothesis of this study was that the vaccine efficacy (VE) of mRNA-1273 to prevent first occurrence of COVID-19 is ≤ 30%, i.e. $H_0^{efficacy}$: VE ≤ 0.3.

The first interim analysis was conducted based on a data snapshot occurred on 11-Nov-2020 whereas the data cut-off date for efficacy was 07-Nov-2020. At IA1, the median follow-up time was 49 days (7 weeks). The primary analysis of COVID-19 is based on the Per-Protocol (PP) set with cases starting 14 days after the 2nd dose. The IA1 efficacy analysis was performed by the independent biostatistician and the results were first reviewed by the independent external DSMB on 15-Nov-2020. The DSMB concluded that

"with 63% of the expected number of the total number of adjudicated primary endpoints, the study has passed the efficacy monitoring boundary for benefit." The DSMB "encourages the study team to prepare the data for the FDA package as rapidly as possible." Based on the DSMB's recommendation, select Sponsor and CRO personnel were unblinded to prepare for regulatory submissions.

Vaccine efficacy of mRNA-1273 was demonstrated at IA1 based on the pre-specified success criterion on efficacy. As efficacy was demonstrated at IA1 based on 95 cases per adjudication committee, all subsequent efficacy analyses, if any, would be considered supportive or supplementary.

At IA1, the total number of COVID-19 starting 14 days after the 2nd injection based on the adjudication committee assessments (i.e. primary efficacy endpoint) was 95, 63% of the information fraction based on the total target number of 151. Correspondingly, the nominal one-sided alpha is 0.0047. At IA1, the one-sided p-value to test null hypothesis of VE $\leqslant$ 30% from the stratified Cox proportional hazard model was <0.0001, and was compared to the nominal one-sided alpha (0.0047) based on the number of cases at IA1 (95 in total). Equivalently, the lower-bound of the alpha-adjusted confidence interval of VE, the two-sided 99.1% CI, can be compared to 30% at IA1. The lower bound of the two-sided 99.1% CI was above 30% at IA1.

6.4.2.2. The Primary Analysis of Efficacy

To support regulatory submissions, in particular, to provide data with a median follow-up duration for safety and efficacy of at least two months after completion of the full vaccination regimen, a decision was made to perform a second analysis based on the data snapshot as of 25-Nov-2020 (DS2, whereas the data cut-off date for efficacy was 21-Nov-2020). Both safety and efficacy analyses were performed to provide additional information on the vaccine's profile. As efficacy has been demonstrated at IA1, the analysis of efficacy based on the data snapshot of 25-Nov-2020 were supplementary in nature.

The date cutoff date for efficacy in the second analysis of efficacy was 21-Nov-2020. All potential COVID-19 cases starting 14 days after the 2nd injection confirmed by RT-PCR

(central or local), with corresponding minimal clinical data in electronic data capture (EDC) as of 21-Nov-2020 were sent to the Adjudication Committee. All these potential cases have been adjudicated for this analysis.

It was anticipated that the total number of COVID-19 cases based on the adjudication committee assessments starting 14 days after the 2nd injection in the Per-Protocol Set at DS2 on 25-Nov-2020 would be ≥ 151, the target total number of events at the originally planned primary analysis. Therefore, this analysis was considered the primary analysis of efficacy of at least 151 cases, as prespecified in the protocol. At DS2, the total number of COVID-19 cases based on the adjudication committee assessments starting 14 days after the 2nd injection in the Per-Protocol Set was 196.

6.4.3. Final Analysis of Efficacy for blinded phase

Results from DS1 and DS2 were used to support EUA application in US and other regions of the world. EUA was authorized for mRNA-1273 in US on 18-December-2020.

The clinical study protocol (CSP) Amendment 6, dated 23-December-2020, informs all ongoing study participants of the availability of and eligibility criteria of any COVID-19 vaccine made available under an EUA and offers participants who originally received placebo in this study the potential benefit of vaccination against COVID-19, given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met per the protocol-defined interim analysis. Participants in this study will have a participant decision visit, at which participants would have the opportunity to be unblinded, and those originally randomized to placebo would have the opportunity to receive mRNA-1273 in this study.

A final efficacy analysis is planned to provide final efficacy update based on data from the blinded phase (Part A) of the study when approximately 90% of the study participants have had the participant decision visit or have been unblinded or discontinued from the study. At this final efficacy analysis of the blinded phase of the study, efficacy data up to the earlier of participant decision visit or unblinding visit, or data cutoff date for efficacy will be included in the analysis.

The analysis period of the blinded phase (Part A) for efficacy analyses will be used:

Part A Treatment Group	Description	Blinded/Part A Analysis Period for Efficacy
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase	From randomization to earlier date of (PDV/unblinding, study discontinuation, study completion, death, or data cutoff for efficacy)
Placebo	Participants randomized to Placebo in the Blinded Phase	From randomization to earlier date of (PDV/unblinding, study discontinuation, study completion, death, or data cutoff for efficacy)

At the time of the final analysis of efficacy for blinded phase date, summary of COVID-19 cases occurred during the open-label phase may be provided.

6.5. Multiplicity Adjustments

The overall type I error rate for this study is controlled at 2.5% (one-sided). The overall Type I error rate for the primary efficacy endpoint at the IAs and the primary analysis is strictly controlled at 2.5% (1-sided) based on the Lan-DeMets O'Brien-Fleming approximation spending function. The primary efficacy endpoint will be considered statistically significant after consideration of the strategy for controlling the Type I error as described in Section 6.4 Interim Analyses. Statistical significance of the primary efficacy endpoint can be achieved at either one of the interim analyses or at the primary analysis.
A sequential/hierarchical testing procedure will be used to control type 1 error rate over the primary efficacy endpoint and the secondary efficacy endpoints. Secondary efficacy endpoints will only be tested when the primary efficacy endpoint achieves statistical significance.
If the primary efficacy endpoint achieves statistical significance at either one of the interim analyses or at the primary analysis, a fixed-sequence statistical strategy will be used to test the following secondary efficacy endpoints in a pre-defined order:

1. secondary efficacy endpoint: COVID-19 regardless of evidence of prior SARS -CoV-2 infection at the same analysis (through the same follow-up period)

2. secondary efficacy endpoint: infection regardless of symptomatology or severity at the same analysis (through the same follow-up period)
3. secondary efficacy endpoint: severe COVID-19 at the analysis with ≥ 20 cases, otherwise, to test at the end of the study

If the primary efficacy endpoint achieves statistical significance at either one of the interim analyses or at the primary analysis, sequential tests of the above 3 secondary efficacy endpoints will be performed at one-sided Type I error rate of 0.025.

All hypothesis tests against the above three secondary efficacy endpoints will be first against a VE ≤ 0% null hypothesis. If hypothesis test against VE ≤ 0% are rejected for all three, sequential testing against a VE ≤ 10% for these three secondary efficacy endpoints will be performed in the same order; if hypothesis test against VE ≤ 10% are rejected for all three, sequential testing against a VE ≤ 20% for these three secondary efficacy endpoints will be performed in the same order; if hypothesis test against VE ≤ 20% are rejected for all three, sequential testing against a VE ≤ 30% for these three secondary efficacy endpoints will be performed in the same order. No further testing will be performed once the sequence breaks, that is, further testing stops as soon as an endpoint in the sequence fails to show significance against corresponding null hypothesis.

No further testing will be performed once the sequence breaks, that is, further testing stops as soon as an endpoint in the sequence fails to show significance against corresponding null hypothesis regarding VE.

While achieving vaccine efficacy that rules out a lower bound of 30% against COVID-19 is the goal of the study, there is utility in formally assessing VEs that are less than 30%. Therefore, in the situation that the primary efficacy endpoint (VE against COVID-19) does not achieve statistical significance against a VE ≤ 30% null hypothesis at neither the interim analyses nor the primary analysis, at the primary analysis, sequential testing against a VE ≤ 20%, a VE ≤ 10%, and a VE ≤ 0% will be performed, halting when a rejection occurs. Figure 2 below demonstrates the testing strategy in this study:

Figure 2: Testing Strategy of Primary and Secondary Efficacy Endpoints

At the first interim analysis where vaccine efficacy for COVID-19 has been demonstrated at the pre-specified statistical criterion, there were 11 total severe COVID-19 cases based on adjudication committee starting 14 days after the 2nd injection.
At the time of IA1 and the primary analysis of efficacy, data for secondary efficacy endpoint infection regardless of symptomatology or severity were not available and were not included in these analyses.

6.6. 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, 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 with modifications for solicited ARs as presented in Table 4 of the study 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 treatment group, unless otherwise specified. Unless specified otherwise, the language in this section pertains to Part A.

6.6.1. Unsolicited Treatment-emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not present before exposure to the IP or any event already present that worsens after exposure to study vaccine. 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.

Unsolicited AEs will be collected for up to 28 days after each IP dose; SAEs, MAAEs, AEs leading to withdrawal will be collected throughout the study. Analyses of unsolicited AE will be provided for up to 28 days after any vaccination unless otherwise specified; and select analyses of unsolicited AE will be provided for Surveillance stage, and overall stage (Section 6.1).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT or by PT only 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 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. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

Unsolicited TEAE will be summarized up to 28 days after any injection. Unsolicited TEAEs may be summarized throughout the study and will be referred to as Overall stage (Part A), defined as from the first dose of study IP to the earlier date of (study discontinuation, study completion, death, data cutoff for safety, PDV/unblinding) for those who did not receive study IP in Part B; or from the first dose of study IP to the earlier date of (study discontinuation, study completion, death, data cutoff for safety, or 1st dose of study IP in Part B) for those who received study IP in Part B.

For AE events (Preferred Terms) with at least 7 participants in any treatment group who report the event, rate ratio and its 95% CI will be provided as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo. The 95% CI for rate ratio will be provided using the Miettinen and Nurminen

method (1985). The threshold of at least 7 participants was chosen because the 95% CI for rate ratio will always include one when groups of equal size each have <7 participants reporting the event, and thus would add little for review purpose.

Percentages will be based upon the number of subjects in the Safety Set within each treatment group.

6.6.1.1. Overview of Unsolicited TEAEs

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

- Any unsolicited TEAEs
- Any serious AEs
- Any unsolicited AEs that are medically-attended
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs (severity of AEs is assessed as mild, moderate and severe)
- 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.

The overall summary will be provided for unsolicited TEAE up to 28 days after any injection, and for the Overall Stage throughout Part A respectively.

In addition, separate listings containing individual subject adverse event data for unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, serious treatment-related AEs, and unsolicited treatment-related medically-attended AEs may be provided. Listing of deaths including cause of death, and listing of TEAEs in subjects who died will be provided.

6.6.1.2. 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 (i.e. number and percentage of subjects with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious AEs
- All serious AEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- 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 AEs that are medically-attended

Summary tables of all unsolicited TEAEs, Serious AEs, treatment-related SAEs, MAAEs, and TEAE leading to discontinuation from participation in the study will be also be provided by SOC and PT for the Overall Stage

6.6.1.3. TEAEs by Preferred Term

The following summary tables of TEAEs will be provided by PT sorting by frequency on the mRNA-1273 group:

- All unsolicited TEAEs

6.6.1.4. TEAEs by Toxicity Grade

The following summary tables of TEAEs will be provided by the maximum Toxicity Grade using frequency counts and percentages:

- All unsolicited TEAEs

- All unsolicited TEAEs that are treatment-related

6.6.1.5. Subgroup Analysis of TEAEs

An overview of TEAE, TEAE summaries presented by SOC and PT will be provided for the following subgroups:

- Age group (<65, and ≥ 65 years)
- Sex (male, female)
- Baseline SARS-CoV-2 status

These summaries may be provided for subgroups of select baseline characteristics.

6.6.1.6. Summary of AEs in Part B at the Final Analysis of Blinded Data

In Part B, for participants who were randomized to Placebo and requested mRNA-1273, SAE, MAAEs, and AE leading to withdrawal are collected throughout Part B.

At the time of the final analysis of blinded data (from the blinded phase of the study) (Section 6.4.3), in addition to the planned analysis of safety for the blinded phase (Part A), summary of SAE, MAAEs, and AE leading to withdrawal in Part B may be provided. The summary will be provided using the Part B groups during the Part B analysis period for safety as described in the table below.

Table 5: Part B groups and analysis period for safety

Part B Cohort	Description	Part B Analysis Period for Safety
mRNA-1273	Participants received at least one dose of mRNA-1273 in the Blinded Phase	From PDV/unblinding to earlier (data cutoff date for safety, last observed in Study). If a participant received mRNA-1273 in Part B, from 1st date of study IP in Part B to earlier date of (data cutoff date for safety, last observed in Study).
Placebo	Participants only received Placebo in the Blinded Phase and did not receive mRNA-1273 in Part B	From PDV/unblinding to earlier date of (data cutoff date for safety, last observed in Study)

Placebo-mRNA-1273	Participants only received Placebo in the Blinded phase and received mRNA-1273 in Part B	From first dose of mRNA-1273 in Part B to earlier date of (data cutoff date for safety, last observed in Study)

6.6.2. 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 subject during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist in the eDiary (i.e. solicited ARs).

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

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

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

If a solicited local or systemic AR continues beyond 7 days post injection, the subject 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.

Analyses of solicited ARs will be provided by 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; and for any injection based on the Solicited Safety Set, 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 provided by severity grade. The number and percentage of subjects who reported each individual solicited AR will also be summarized by severity grade, days 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 and the number and percentage of subjects experiencing a fever of Grade 3 or higher temperature (a temperature greater than or equal to 39.0°C/102.1°F by the oral, axillary, or tympanic route) will be provided.

A two-sided 95% exact 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 study day relative to the corresponding injection (Day 1 through Day 7).

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 (e.g. 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.)

All solicited ARs that continue beyond 7 days post injection will be summarized.

The above analyses of solicited ARs will be provided for the following subgroups:

- Age group (<65, and ≥ 65 years)
- Sex (male, female)
- Baseline SARS-CoV-2 status

These summaries may be provided for subgroups of select baseline characteristics.

6.6.3. 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 baseline SARS-CoV-2 serostatus and treatment group as defined in Section 6.1. Shift from baseline in the toxicity grades may be summarized at each visit by treatment group.

In addition, summary of pregnancies and outcome will be provided by treatment group. A listing of pregnancies including outcome will be provided.

6.7. Immunogenicity Analysis

There are two objectives on immunogenicity in this study: to characterize the immunogenicity of mRNA-1273 (secondary objective) and to assess correlates of risk and protection (exploratory objective).

This SAP includes analyses of immunogenicity data for the secondary immunogenicity objective: To evaluate the immunogenicity of 2 doses of mRNA-1273 given 28 days apart.

The analysis of assessing correlates of risk and protection will be included in a separate Immune Correlates SAP.

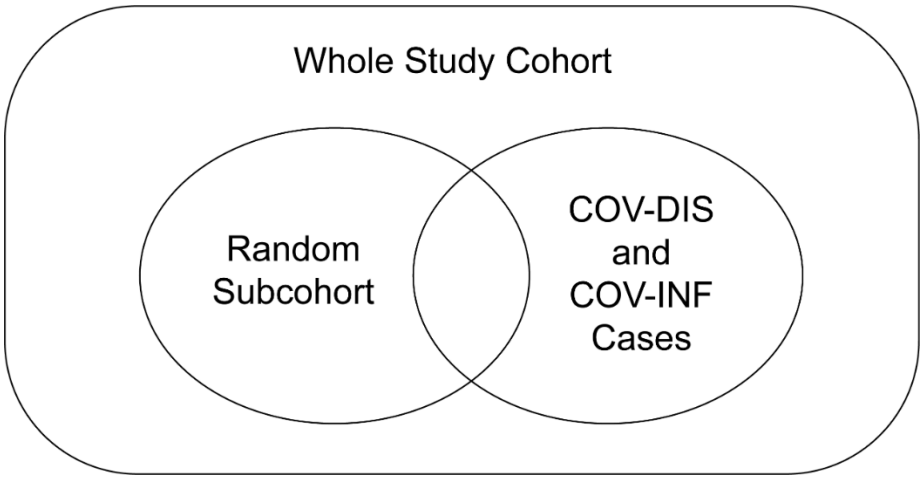
6.7.1. Sampling of the Immunogenicity Subset (Case-cohort Sampling Design)

For characterizing immunogenicity of the vaccine, and for assessing correlates of risk and protection (CoR/CoP), a case-cohort sampling design will be used for measuring bAb and nAb data from a randomly sampled subset of trial participants [the case-cohort Immunogenicity Analysis Set (ccIAS)], or Immunogenicity Subset. The ccIAS cohort consists of a stratified random sample of trial participants (Random SubCohort), augmented with a subset of all primary endpoint cases and SARS-CoV-2 infection endpoint cases. The immunogenicity samples of the ccIAS cohort will be processed and the immunogenicity data will be available for the ccIAS cohort.

A case-cohort sampling design (Prentice (1986)) is used for measuring antibody markers in a random sample of study participants and from all or a subset of cases of COVID-19 primary endpoint (COV-DIS) and infection endpoint (COV-INF) (Figure 3). The random sample is stratified by the key baseline characteristics: assigned treatment arm, baseline SARS-CoV-2 status (defined in Section 6.1), stratification factor used for randomization, and minority (defined as Race being Blacks or African Americans, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders; or Ethnicity being Hispanics or Latinos).

This design uses a stratified random sample instead of the simple random sample proposed by Prentice (1986), the design may also be referred to as a two-phase sampling design, where “phase one” refers to variables measured in all participants and “phase two" refers to variables only measured in a subset (thus the “case-cohort sample" constitutes the phase-two data, e.g. antibodies).

Figure 3: **Case-cohort sampling design: participants selected into the stratified random sample (Random Subcohort) and in all or a subset of COVID-19 and COV-INF cases occurring outside of the Random Subcohort.**



The Immunogenicity Subset will be used to characterize immunogenicity of mRNA-1273, and to assess correlates of risk and protection. The analysis of characterizing immunogenicity of mRNA-1273 is included in Section 6.7 of this SAP; the analysis of assessing correlates of risk and protection will be included in a separate Immune Correlates SAP.

Eligibility criteria for Immunogenicity SubSet

For stratified random sample:

Only participants in the FAS Set with non-missing key baseline characteristics for the strata, and with serum samples available at both Day 1 (baseline) and Day 57 are eligible for sampling into the stratified random sample (Random Subcohort).

Adjudicated COVID-19 cases and COV-INF cases:

Correlates of Risk (CoR) and Correlates of Protection (CoP) analysis will be documented in a separate Immune Correlates SAP. For CoR/CoP analysis, adjudicated COVID-19 primary endpoint cases (section 6.3.1.1) regardless of baseline SARS-CoV-2 status,

infection cases on mRNA-1273 regardless of baseline SARS-CoV-2 status, and adjudicated COVID-19 cases and infection cases on Placebo in participants with baseline positive SARS-CoV-2 status are eligible to be included regardless of the time of their event date.

Sample size for the stratified random sample (Random Subcohort)

Table 6 describes the numbers of participants sampled into the stratified random sample (Random Subcohort), for each of the 24 sampling strata defined by randomization arm, baseline SARS-CoV-2 status, stratification factor used for randomization (Age ⩾ 18 and < 65 years and not at risk, ⩾ 18 and < 65 years and at risk 18-64 not 'at risk', Age ⩾ 65), and minority status. Participants are randomly sampled into the Random Subcohort within each of the strata. This sampling design enables characterization immune response (bAb and nAb readouts) in all relevant subgroups. The sampling is implemented without replacement. A sampling list for the Random Subcohort was planned to be generated after all baseline characteristics for the strata were available and most of the participants have completed the Day 57 visit or discontinued the study.

Table 6 summarizes the size of the Random Subcohort, by baseline factors used to stratify the random sampling. For each of the mRNA-1273 and placebo arms, if any of the 6 baseline SARS-CoV-2 positive strata have fewer than 60 participants enrolled such that it is not possible to sample 60 participants, then all participants in the stratum will be sampled.

Table 6: Random Subcohort Sample Sizes by Baseline Strata

	Baseline SARS-CoV-2 Negative (Total N=1224)						**Baseline SARS-CoV-2 Positive (Total N=720)**					
Baseline Covariate Strata[1]	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Planned Evaluable participants (Total N=1620)												
mRNA-1273	150	150	150	150	150	150	50	50	50	50	50	50

Placebo	20	20	20	20	20	20	50	50	50	50	50	50
Adjusting for approximately 15% participants who may be excluded from the Per-protocol Subcohort for immunogenicity (Total N=1944)												
mRNA-1273	**180**	**180**	**180**	**180**	**180**	**180**	**60**	**60**	**60**	**60**	**60**	**60**
Placebo	**24**	**24**	**24**	**24**	**24**	**24**	**60**	**60**	**60**	**60**	**60**	**60**

1 = ⩾ 18 and < 65 years and not at risk, Minority; 2 = ⩾ 18 and < 65 years and at risk, Minority; 3 = Age ⩾ 65, Minority; 4 = ⩾ 18 and < 65 years and not at risk, non-Minority; 5 = ⩾ 18 and < 65 years and at risk, non-Minority; 6 = Age ⩾ 65, non-Minority

6.7.2. Per-Protocol Random Subcohort for Immunogenicity

The Per-Protocol Random Subcohort for Immunogenicity (PPRSI) will be used as the analysis population to characterize immunogenicity of mRNA-1273. The Per-Protocol Subcohort for immunogenicity consists of participants in the FAS who are sampled into the Random Subcohort and

a). received both planned doses (i.e. received the treatment as the participant was randomized to) with dose 2 received within [21, 42] days after dose 1, and

b). no major protocol deviation that impact critical or key data.

A subset of the planned Random Subcohort that is representative of the Random Subcohort may be used to expedite analyses to characterize immunogenicity of mRNA-1273.

6.7.3. Immunogenicity Data

The following immunogenicity assessments (assays) may be used in this study:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 S protein (vaccine antigen), tests may include VAC65 Spike IgG Antibody.
- The MSD-ECL Multiplex Assay (MSD-ECL = meso scale discovery – electrochemiluminescence assay) measures binding antibody to antigens corresponding to: Spike; the Receptor Binding Domain (RBD) of the Spike protein; and Nucleocapsid protein (NP), which is not contained in mRNA-1273.

- Pseudovirus nAb assay for measuring neutralizing antibodies against SARS-CoV-2 Spike-pseudotyped viruses: Pseudovirus neutralizing antibody ID50 and ID80 titers (PsVNT50 and PsVNT80)
- Wild Type Live virus-nAb assays measuring antibody-mediated neutralization of live wild-type SARS-CoV-2 (Wild Type Live virus-nAb MN [microneutralization] 50 titers)

6.7.4. Summary of Antibody-Mediated Immunogenicity Endpoints

Data from quantitative immunogenicity assays will be summarized for each treatment group using positive response rates and geometric means with 95% CI at each timepoint when an assessment is performed. Data from qualitative (i.e., yielding a positive or negative result) assays will be summarized by tabulating the frequency of positive responses for each assay by treatment group and by baseline status based on bAb specific to SARS-CoV-2 NP as measured by *Roche Elecsys* SARS-CoV-2 assay, if applicable, at each timepoint that an assessment is performed.

At the time of the final blinded efficacy analysis, immunogenicity analysis to characterize immunogenicity of mRNA-1273 may be performed. At the time of immunogenicity analysis, data for bAb to Spike (MSD, PPD-VAC65), RBD (MSD); and Pseudovirus neutralizing antibody ID50 and ID80 titers are expected. The assay by MSD to measure bAb against RBD may not have been validated yet at the time of the immunogenicity analysis, in that situation, bAb against RBD by MSD will not be summarized/analyzed. Immunogenicity data at the pre-specified timepoints: baseline (Day 1), Day 29 and Day 57 will be included.

- Geometric mean titer (GMT) or value 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.

- Geometric mean fold rise (GMFR) with corresponding 95% CI will be provided at each post-baseline 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. GMFR 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.
- Reverse cumulative distribution function curve (RCDF) at each time point. The number and percentage of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 from Baseline at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs. If assay-specific fold rise criteria are available, the number and percentage of subjects with fold-rise exceeding the criteria with 95% CI will be provided instead.
- Proportion of subjects with seroconversion due to vaccination will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint. Seroconversion due to vaccination at a subject level may be defined as a change from below the LLOQ to equal to or above LLOQ, or 4-fold rise if baseline is equal to or above LLOQ. The definition of seroconversion may depend on assay-specific performance characteristics and the final definition of seroconversion due to vaccination will be documented in a memo.

The GMT and GM levels will be calculated using the following formula:

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

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

The geometric mean fold rise (GMFR) measures the changes in immunogenicity titers 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, $j \neq k$.

6.7.5. Analysis of Antibody-Mediated Immunogenicity Endpoints

To assess the magnitudes of the differences between the two treatment groups (mRNA-1273 vs. Placebo) in SARS-CoV-2-specific nAb and S protein-specific bAb, a mixed model for repeated measures (MMRM) using SAS PROC MIXED will be used.

For each of the SARS-CoV-2-specific nAb and S protein-specific bAb, the analysis will be performed separately for subjects who are seropositive and seronegative (as measured by Roche Elecsys SARS-CoV-2 assay) at baseline respectively. The model will include all available log-transformed antibody titers at each post-baseline visit as the dependent variable, treatment groups, visit (as a class variable), and treatment-by-visit interaction visit as fixed effects, with adjustment for stratification factor used for randomization, baseline log-transformed anti-body titers if applicable, and subject as a random effect. The model may also adjust for minority group used to sample for the random subcohort. An unstructured covariance structure will be used to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence issue due to the unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. No imputation of missing data will be done.

The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the anti-body titers for each treatment group will be provided by visit. The GLSM, and corresponding 95% CI results in log-transformed scale estimated from the model will be

back-transformed to obtain these estimates in the original scale. Geometric mean ratio (GMR), estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference between mRNA-1273 group vs. placebo group at each visit. With each treatment group, within-group comparison of timepoints may also be estimated using the same model.

In addition, an analysis of covariance (ANCOVA) model with the treatment group as explanatory variables, adjusting for the stratification factor at randomization, baseline value if applicable, will be used to assess the treatment effect at specific timepoints (scheduled visits) such as Day 57. GLSM with 95% CI for each treatment group, GMR with 95% CI for treatment difference will be estimated from the ANCOVA model. The model may also adjust for minority group used to sample for the random subcohort.

6.7.6. Summary of Immunogenicity in COVID-19 Cases on mRNA-1273 with negative SARS-CoV-2 status at baseline

To characterize immunogenicity of mRNA-1273, immunogenicity data (Section 6.7.3) will be analyzed using the Per-Protocol Random Subcohort for Immunogenicity.
It is of interest to examine the immune response in subjects on mRNA-1273 with baseline SARS-CoV-2 negative status who were COVID-19 or SARS-CoV-2 infection cases. Summary of immunogenicity may be provided in a subset of baseline SARS-CoV-2 negative participants on mRNA-1273 who were COVID-19 cases based on adjudication committee assessments.

6.8. Exploratory Analysis of Efficacy

Exploratory analyses of efficacy described in this section will not be performed at the interim analyses, and may be performed at the primary analysis, with the exception of exploratory analyses of Burden of Disease (BOD) and Burden of Infection (BOI) that will be performed at the interim analyses and provided to the DSMB.

6.8.1. Vaccine Efficacy Against Burden of Disease

Exploratory analysis of BOD due to COVID-19 will be performed. A BOD score is defined based on the post SARS-CoV-2 infection follow-up to reflect the worst severity of symptoms as shown in the table below.

Table 7: Burden of Disease Score

Subject State (Worst Category Following Disease Detection)	**BOD Score**
Without COVID-19 (uninfected/asymptomatic infection)	0
COVID-19 without hospitalization (symptomatic without hospitalization)	1
COVID-19 with hospitalization	2
Death	3

Summary of BOD score, number and percentage of subject with each level of BOD score, will be provided by treatment group using the PP Set. A t-test of the BOD scores may be performed to compare mRNA-1273 vs. placebo group.

To assess impact of baseline risk of severe disease on the vaccine effect regarding disease severity, summary of BOD may be provided by randomization strata (i.e. ≥ 65 years, < 65 years at risk, and < 65 years not at risk).

In order to assess the disease burden in subjects with COVID-19, the above analyses may also be performed in participants with COVID-19, i.e. subjects with BOD score of zero will be excluded from the analysis.

While transparent, the proportions in the summary table will change with increased follow-up time as more subjects inevitably acquire disease. This makes comparisons across

different periods of follow-up difficult. To augment this analysis, a proportional means model will be used to assess the treatment effect on BOD between mRNA-1273 and placebo in terms of ratio of mean severity score. The proportional means model allows for direct comparisons across different periods of follow-up, unaffected by differential follow-up. A proportional means model including vaccination group as fixed effect and stratified with stratification factor at randomization will be used to assess the vaccine effect on BOD. The VE for the BOD score will be estimated as 1 minus the ratio of means as estimated by the proportional means model and reported with 95% confidence intervals.

6.8.2. Vaccine Efficacy Against Burden of Infection

To fully understand the impact of vaccination on disease severity, asymptomatic infections should also be evaluated. Similarly, a burden of infection (BOI) score will be calculated as in the table below and used to understand the impact. Because asymptomatic infection is identified by seroconversion only at scheduled visits at which samples for RT-PCR test and/or serum samples will be taken (e.g. months 1, 2, 7, 13 and 25), summary of BOI will be provided for relevant periods (e.g. Baseline through M1, M1 through M2, M2 through M7, M7 through M13, and M13 through M25) only using subjects who have serological data for that period. With protocol amendment 6, at the unblinding/participant decision visit/Open-label-Day 1 (OL-D1) visit, NP swab for RT-PCR tests and serum samples will be taken. The relevant periods will be updated to Baseline through M1, M1 through M2, M2 through M7/OL-D1 whichever is earlier.

A t-test of the BOI scores may be performed to compare mRNA-1273 vs. placebo group. A proportional means model including vaccination group as fixed effect and stratified with stratification factor at randomization will be used to assess the vaccine effect on BOI. The VE for BOI will be estimated as 1 minus the ratio of mean BOI scores and reported with 95% confidence intervals.

Table 8: Burden of Infection Score

Patient State (Worst Category Following Disease Detection)	**BOI Score**
No infection	0
Asymptomatic infection	1/2
COVID-19 without hospitalization (Symptomatic without hospitalization)	1
COVID-19 with Hospitalization	2
Death	3

6.8.3. Vaccine Efficacy on Duration and Presence/Severity of COVID-19 Symptoms

Subjects will report symptoms including fever (temperature ≥ 38ºC), chills, cough, shortness of breath, difficulty breathing, fatigue, muscle aches (myalgia), body aches, headache, new loss of taste, new loss of smell, sore throat, nasal congestion, runny nose (rhinorrhea), nausea, vomiting, and diarrhea. The severity scoring system of the symptoms is presented in the table below. A score endpoint aggregating duration and presence/severity of COVID-19 symptoms may be calculated as the sum of daily severity scores of all recorded symptoms across all days with symptoms. The VE of mRNA-1273 based on mean score of each treatment group will be calculated as below:

VE = [1 – Mean score of mRNA-1273 group / Mean score of placebo group] × 100%

Table 9: Grading of COVID-19 Symptoms

Grading	All Symptoms	For Nausea/Vomiting ONLY	For Sense of Smell/Taste ONLY	Score
None	No symptom			0
Mild	I had the symptom, but I could still do my normal activities	I was able to eat and drink normally	I had the symptom, but I retained some taste/smell	1
Moderate	The symptom really bothered me. It was hard to do my normal activities.	It bothered me enough that I did not eat or drink normally.	My taste/smell was significantly affected.	2
Severe	The symptom was very bad. I was not able to do activities that I usually do.	I could not eat or drink.	I have no taste or smell.	3

A proportional means model including vaccination group as fixed effect and stratified with stratification factor at randomization will be used to assess the VE (mRNA-1273 vs. placebo) on the score aggregating duration and presence/severity of COVID-19 symptoms based on the PP Set. The score will be summarized and categorized into quartiles (across the two groups) using 1, 2, 3, 4. The indication of the quartiles will be used as the dependent variable in the proportional mean model.

6.8.4. Vaccine Efficacy Against All-cause Mortality

To evaluate VE against all-cause mortality, the same Cox PH model described above based on the PP Set, mITT Set, and FAS will be used. Death, regardless of cause, from randomization will be included. Time to death will be calculated as date of death – date of randomization + 1. At the final analysis of blinded data, subjects with no documented death will be censored.

6.8.5. Vaccine Efficacy Against COVID-19 Over Time

For exploratory analysis of the VE on the COVID-19 primary endpoint over time, to assess if there is any time trend of the effect of the vaccine, e.g. if the effect of the vaccine is waning over time during the follow-up, an extended Cox model with an addition of a covariate incorporating interaction of time by treatment group may be carried out.

For exploratory analysis of the VE on the COVID-19 primary endpoint over time, the instantaneous hazard ratio (mRNA-1273 vs. placebo) of the endpoint may be estimated with pointwise and 95% confidence intervals, using nonparametric kernel smoothing estimation of each of the mRNA-1273 and placebo arm hazard functions over time, using the method of Gilbert *et al*. (Gilbert, 2002) with optimal bandwidths selected using the analytical formula in Andersen *et al*. (Andersen, 1993). At each interim analysis, a plot of the hazard ratio results, as well as plots of the point estimates and pointwise and simultaneous 95% confidence interval estimates for the treatment-arm specific hazard functions, may be provided.

6.8.6. Durability of Vaccine Efficacy Against COVID-19

Durability of vaccine efficacy will be assessed by the incidence rate of COVID-19 by time periods.

As an exploratory analysis to assess durability of VE against the primary endpoint, covariate adjustment method based on cumulative incidence may be used. Cumulative incidence VE may be assessed using a parameter $VE_{CI}(0-t)$, defined as one minus the ratio of cumulative incidences (mRNA-1273 vs. placebo) of the COVID-19 endpoint over

follow-up through time *t* post enrollment. All times *t* ranging from 0 to *t** will be considered, where *t** is defined as the final time through which at least 1,000 subjects are at risk for the COVID-19 endpoint. The cumulative incidence for each vaccination group will be estimated using a covariate adjustment method based on Zeng (2004) that makes use of baseline subjection information. These covariates will include demographic information such as age, sex, and race/ethnicity, and stratification factor at randomization. The most useful covariates to adjust for in producing potential efficiency gains are potential modifiers of VE.

The covariate adjustment method that will be used is more robust than unadjusted approaches (e.g., the Kaplan-Meier estimator), as it yields valid inferences even in cases in which loss to follow-up is informative, provided within each intervention arm the possible relationship between censoring and the COVID-19 endpoint can be explained by observed baseline covariates. Unadjusted methods, in contrast, can give biased answers in this setting, which manifests as 95% confidence intervals that contain the true VE less than 95% of the time, or as tests of the null H_0: VE ≤ 30% that reject with probability greater than the specified type 1 error level. Also, the covariate adjustment method often results in more precise estimates when available baseline covariates (e.g. stratification factor at randomization) are predictive of the COVID-19 endpoint, thereby yielding tighter confidence intervals for the cumulative VE and higher-powered tests of the null hypothesis. This efficiency gain may be especially pronounced in settings where the randomization is not stratified on factors such as age category or trial site.

The estimator for the survival function in arm v (mRNA-1273 or placebo) that adjusts for baseline covariates L is implemented using the following steps:

1. (a) Using only data from arm v, fit a main terms Cox regression to estimate the hazard of the COVID-19 endpoint conditionally on L. Refer to the fitted vector of coefficients as $\hat{\beta}$.

(b) Repeat step (a), but estimate the hazard of *censoring* conditionally on L. Refer to the fitted vector of coefficients as $\hat{\gamma}$.

2. For given coefficient $\hat{\alpha}$ (= $\hat{\beta}$ or $\hat{\gamma}$) and a given covariate value ℓ, let $f_{\hat{\alpha}}(\ell)$ denote the $j \in 1, \ldots, 4$ for which $q_{\hat{\alpha},j-1} < \hat{\alpha}^\top \ell \leq q_{\hat{\alpha},j}$, where $q_{\hat{\alpha},1}, q_{\hat{\alpha},2}, q_{\hat{\alpha},3}$ denote the empirical quartiles of $\hat{\alpha}^\top L$ in arm v and $q_{\hat{\alpha},0} = -\infty$ and $q_{\hat{\alpha},4} = \infty$.
3. Using only data from arm v, fit a stratified Kaplan Meier using the COVID-19 endpoint as outcome within all non-empty strata of $(f_{\hat{\beta}}(L), f_{\hat{\gamma}}(L))$ – there will be at most 16 such strata. If any strata are empty, estimate the survival function within those strata as the constant function 1.
4. Estimate the arm-specific survival function by taking a weighted average across the 16 strata, where each stratum-specific survival function receives weight equal to the empirical probability of a randomly selected Subject (from either the vaccine or placebo arm) having baseline covariates belonging to that stratum.

Estimates of the arm-specific cumulative incidences and cumulative incidence VE are obtained by transforming the estimated arm-specific survival functions. Missing covariates will be accounted for using median imputation, which preserves the randomization of treatment even given imputed covariates.

The validity of this estimator relies on the condition that, within all strata of L, there must be a positive probability that a Subject will have follow-up through time t^*. As such, covariates such as trial site should not be included in if the enrollment timeline is such that this condition fails to hold.

Two-sided Wald-based 95% confidence intervals for a log-transformed cumulative incidence ratio estimate will be provided, and these intervals will be transformed to yield intervals for $VE_I(0-t)$, $t \in [0, t^*]$. Accompanying uniform confidence bands, constructed using the multiplier bootstrap with Rademacher weights (Kosorok 2007), will also be provided. The covariate-adjusted arm-specific cumulative incidence estimates will also be plotted over time, with confidence intervals and uniform confidence bands defined

by transforming a Wald interval for a complementary log-log transformation of the corresponding survival functions.

6.9. Summary of Protocol Safety Review and Data Safety Monitoring Board

6.9.1. Protocol Safety Review Team

A Protocol Safety Review Team (PSRT) will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the DSMB. The PSRT will be composed of the study's three coordinating investigators and representatives from Moderna, National Institute of Allergy and Infectious Diseases (NIAID), Biomedical Advanced Research and Development Authority (BARDA), and the CRO. The PSRT composition, its remit, and the routine and systematic procedures for safety review and oversight of blinded interval and cumulative data during the mRNA-1273 P301 study by the PSRT is documented in the Moderna mRNA-1273 P301 Protocol Safety Review Team Charter.

6.9.2. Data Safety Monitoring Board (DSMB)

The Coronavirus Disease 2019 (COVID-19) Vaccine Data and Safety Monitoring Board (DSMB) will monitor all randomized COVID-19 vaccine studies supported by the United States Government (USG). The independent DSMB will periodically review blinded and unblinded data of mRNA-1273-P301, including

- continuous monitoring for potential vaccine harm and non-efficacy based on imbalance between mRNA-1273 vs. placebo for both COVID-19 and severe COVID-19 case counts.
- regular review of safety data at scheduled data review meetings
- review the two planned interim analyses

The statistical considerations and methods for DSMB is documented in the Analysis Plan for DSMB (current version: Version 2.0 dated 07-August-2020).

6.9.2.1.Potential Vaccine Harm

The DSMB has continuously monitored potential vaccine harm in this study. Potential vaccine harm is assessed based on imbalance between mRNA-1273 vs. placebo for both COVID-19 and severe COVID-19 case counts using the Safety Set. For harm monitoring, subjects are analyzed according to the IP that they actually received regardless of the group to which they were randomized. For harm monitoring, cases are counted starting after the first dose of study vaccination.

Cases of COVID-19 for the harm monitoring are defined as for the primary efficacy endpoint (eligible symptoms with positive RT-PCR result) but are based on the Safety Set rather than the PPS. For harm monitoring, cases of COVID-19 are derived based on RT-PCR results and symptoms collected in the clinical database to facilitate continuous monitoring.

Details of harm monitoring are provided in the analysis plan for DSMB. The monitoring for potential harm based on COVID-19 would continue to the first interim analysis, and the DSMB can decide how to continue; the harm monitoring for potential harm based on the number of severe COVID-19 cases would continue at least until the primary analysis.

DSMB recommended discontinuation of the harm monitoring reports to the DSMB after the DSMB review meeting on 29-Jan-2021. Thus, harm monitoring is considered completed and discontinued per DSMB recommendation effective immediately.

7. Changes from Planned Analyses in Protocol

Not applicable.

8. References

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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 more significant figure than the original results; the SD will be presented to two more significant figures 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

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

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 10 below. For subjects with confirmed COVID-19, unscheduled assessments will be preferably mapped to the visits with respect to the confirmation of COVID-19 (i.e. Illness Visit Day xx) over nominal scheduled visits (i.e. Day xx).

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 10: Analysis Visit Windows

Visit	Target Study Day	Visit Window in Study Day
Nasopharyngeal swab (or saliva)		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 29	29 (Date of Second Injection)	
Illness Visit Day 1	X (Date of NP Swab test)	X
Illness Visit Day 3	X+2	[X+1, X+2]

Illness Visit Day 5	X+4	[X+3, X+4]
Illness Visit Day 7	X+6	[X+5, X+6]
Illness Visit Day 9	X+8	[X+7, X+10]
Illness Visit Day 14	X+13	[X+11, X+16]
Illness Visit Day 21	X+20	[X+17, X+23]
Illness Visit Day 28	X+27	[X+24, X+34]
Vital Signs		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 1	1 (Date of First Injection)	1, Post-first-dose
Day 29	29 (Date of Second Injection)	[2, 43] Pre-second-dose
Day 29	29 (Date of Second Injection)	[2, 43] Post-second-dose
Day 57	57	[44, 133]
Day 209	209	[134, 301]
Day 394	394	[302, 576]
Day 759	759	[577, 773]
Illness Visit Day 1	X (Date of COVID-19 Confirmation)	X
Illness Visit Day 28	X+27	[X+2, X+34]
Immunogenicity		
Day 1	1	1, Pre-first-dose
Day 29	29 (Date of Second Injection)	[2, 43] Pre-second-dose

Day 57	57	[44, 133]
Day 209	209	[134, 301]
Day 394	394	[302, 576]
Day 759	759	[577, 773]
Illness Visit Day 1	X (Date of NP Swab test)	X
Illness Visit Day 28	X+27	[X+2, X+34]

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

Imputation rules for missing or partial start/stop dates of medication 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 on/after the date of first injection or is missing/partial 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 on/after the date of first injection or is missing/partial 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:

a. If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).

b. 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).

c. 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 medications and non-study vaccinations is described in the table below.

Table 11: 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	-	-	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 Dates of AEs

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

1. Missing or partial start date:

- If only Day is missing, use the first day of the month, unless:
  - The AE end date is on/after the date of first injection or is missing/partial 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 AE time was collected.

- If Day and Month are both missing, use the first day of the year, unless:
  - The AE end date is on/after the date of first injection or is missing/partial AND the start year of the AE coincides with the start year of the first injection. In this case, use the date and time of first injection, when time is available.
- 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 end dates will not be imputed.

9.5. Appendix E Schedule of Events

Please refer to Table 16, 17, 18 and 19 in Appendix 1 Schedule of Events in the protocol.

9.6. Appendix F Estimands and Estimand Specifications

Table 12: Intercurrent Event Types

Label	Intercurrent Event Type	Comment
IcEv1 (early discontinuation or death without confirmation of cases, ie, unrelated death)	Early discontinuation from study preventing from confirmation of COVID-19, ie, unrelated death or withdrawal consent prior to documented confirmed COVID-19	Participants in PP Set who withdraw consent or die due to unrelated to COVID-19 without confirmation of being a case will all be included in primary efficacy analysis.
IcEv2 (early COVID-19)	COVID-19 starting up to 14 days after the second dose of IP	Participants in PP Set who experience an early COVID-19 up to 14 days after the second dose of IP will all be included in primary efficacy analysis.

10. Abbreviation: IcEv: intercurrent event, PP: per protocol.

Table 13: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for Per Protocol Analysis

Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19	
Estimand Description	Vaccine efficacy will be measured using 1 – HR (mRNA-1273/Placebo) of COVID-19 from 14 days after second dose of IP in adults. A hypothetical strategy will be used for early discontinuation (eg, withdrawal consent, deaths unrelated to COVID-19) or early COVID-19 in participants in PP Set..
Target Population	Adults aged 18 years and older in circumstances at a high risk of SARS-CoV-2 infection but without medical conditions that pose additional risk of developing severe disease. The population excludes those previously infected or vaccinated for SARS-CoV-2 or with a medical condition, on treatment that poses additional risks (including those requiring immunosuppressants or immune-modifying drugs), or pre-seropositive.
Variable/Endpoint	Time to COVID-19 disease, censoring at early discontinuation, early COVID-19, or last assessment for an event not being observed, whichever comes earlier.
Treatment Condition(s)	**Test:** mRNA-1273 **Reference:** Placebo
Estimand Label	**Estimand 1**
Population-Level Summary	Vaccine efficacy defined as 1 - HR of mRNA-1273/Placebo
Intercurrent Event Strategy	
IcEv1 (Early discontinuation):	Hypothetical
IcEv2 (early COVID-19):	Hypothetical

Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19

Rationale for Strategy(s)	Hypothetical: early discontinuation (including unrelated death) censored at time of discontinuation (or at time of death), and early case will be censored at the time at case onset, handled with independent censoring.

Client:	**ModernaTX, Inc.**
Protocol Number:	**mRNA-1273-P301**

Document Description:	Statistical Analysis Plan
SAP Title:	A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
SAP Version Number:	2.0
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Signer Name: Weiping Deng
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Brett Leav, MD
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