

**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**

**SAP Version 1.0**

**Version Date of SAP: 10 September 2020**

Prepared by:

PPD  
3575 Quakerbridge Road  
Suite 201  
Hamilton, NJ 08619

Confidential

FDA-CBER-2022-1614-4805806

## TABLE OF CONTENTS

<b>LIST OF ABBREVIATIONS</b>	<b>VI</b>
<b>1. INTRODUCTION</b>	<b>9</b>
<b>2. STUDY OBJECTIVES</b>	<b>10</b>
2.1. PRIMARY OBJECTIVES	10
2.1.1. <i>Primary Efficacy Objective</i>	10
2.1.2. <i>Primary Safety Objective</i>	10
2.2. SECONDARY OBJECTIVES	10
2.2.1. <i>Secondary Efficacy Objectives</i>	10
2.2.2. <i>Secondary Immunogenicity Objective</i>	11
2.3. EXPLORATORY OBJECTIVES	11
<b>3. STUDY ENDPOINTS</b>	<b>12</b>
3.1. PRIMARY ENDPOINTS	12
3.1.1. <i>Primary Efficacy Endpoint</i>	12
3.1.2. <i>Primary Safety Endpoint</i>	12
3.2. SECONDARY ENDPOINTS	13
3.2.1. <i>Secondary Efficacy Endpoints</i>	13
3.2.2. <i>Secondary Immunogenicity Endpoints</i>	14
3.3. EXPLORATORY ENDPOINTS	14
<b>4. STUDY DESIGN</b>	<b>15</b>
4.1. OVERALL STUDY DESIGN	15
4.2. STATISTICAL HYPOTHESIS	18
4.3. SAMPLE SIZE AND POWER	18
4.4. RANDOMIZATION	19
4.5. BLINDING AND UNBLINDING	20
<b>5. ANALYSIS POPULATIONS</b>	<b>21</b>
5.1. RANDOMIZATION SET	21
5.2. FULL ANALYSIS SET	21
5.3. MODIFIED INTENT-TO-TREAT SET	21
5.4. PER-PROTOCOL SET	21
5.5. IMMUNOGENICITY SUBSET	22
5.6. SOLICITED SAFETY SET	22
5.7. SAFETY SET	23

<b>6.</b>	<b>STATISTICAL ANALYSIS</b>	<b>23</b>
6.1.	GENERAL CONSIDERATIONS	23
6.2.	BACKGROUND CHARACTERISTICS	27
6.2.1.	<i>Subject Disposition</i>	27
6.2.2.	<i>Demographics and Baseline Characteristics</i>	29
6.2.3.	<i>Medical History</i>	29
6.2.4.	<i>Prior and Concomitant Medications</i>	30
6.2.5.	<i>Study Exposure</i>	31
6.2.6.	<i>Major Protocol Deviations</i>	31
6.2.7.	<i>COVID-19 Impact</i>	31
6.3.	EFFICACY ANALYSIS	31
6.3.1.	<i>Analysis of Primary Efficacy Endpoint</i>	32
6.3.1.1.	Primary Efficacy Endpoint Definition/Derivation	32
6.3.1.2.	Primary Analysis Approach	34
6.3.1.3.	Sensitivity Analyses with COVID-19 Cases Counted Starting at Various Timepoints	36
6.3.1.4.	Subgroup Analysis	38
6.3.1.5.	Supportive Analysis Using Exact Method Based on Incidence Rate	39
6.3.2.	<i>Analysis of Secondary Efficacy Endpoints</i>	40
6.3.2.1.	Derivation of Severe COVID-19	40
6.3.2.2.	Derivation of Secondary Definition of COVID-19	40
6.3.2.3.	Derivation of Serologically Confirmed SARS-CoV-2 Infection or COVID-19 Regardless of Symptomatology or Severity	41
6.3.2.4.	Derivation of Asymptomatic SARS-CoV-2 Infection	44
6.3.2.5.	Analysis of Secondary Efficacy Endpoints	44
6.4.	INTERIM ANALYSES	46
6.5.	MULTIPLICITY ADJUSTMENTS	48
6.6.	SAFETY ANALYSIS	52
6.6.1.	<i>Unsolicited Treatment-emergent Adverse Events</i>	52
6.6.1.1.	Overview of Unsolicited TEAEs	53
6.6.1.2.	TEAEs by System Organ Class and Preferred Term	54
6.6.1.3.	TEAEs by Preferred Term	54
6.6.1.4.	TEAEs by Toxicity Grade	55
6.6.1.5.	Subgroup Analysis of TEAEs	55
6.6.2.	<i>Solicited Adverse Reactions</i>	55
6.6.3.	<i>Vital Sign Measurements</i>	57
6.7.	IMMUNOGENICITY ANALYSIS	57
6.7.1.	<i>Immunogenicity Data</i>	58
6.7.2.	<i>Summary of Antibody-Mediated Immunogenicity Endpoints</i>	58
6.7.3.	<i>Analysis of Antibody-Mediated Immunogenicity Endpoints</i>	60
6.8.	EXPLORATORY ANALYSIS OF EFFICACY	61
6.8.1.	<i>Vaccine Efficacy Against Burden of Disease</i>	61

6.8.2.	<i>Vaccine Efficacy Against Burden of Infection</i> .....	63
6.8.3.	<i>Vaccine Efficacy on Duration and Presence/Severity of COVID-19 Symptoms</i> 64	
6.8.4.	<i>Vaccine Efficacy Against COVID-19 Over Time Based on Instantaneous Hazard Ratio</i> .....	65
6.8.5.	<i>Durability of Vaccine Efficacy Against COVID-19 Using Covariate Adjustment Method Based on Cumulative Incidence</i> .....	65
6.9.	SUMMARY OF PROTOCOL SAFETY REVIEW AND DATA SAFETY REVIEW BOARD .....	68
6.9.1.	<i>Protocol Safety Review Team</i> .....	68
6.9.2.	<i>Data Safety Monitoring Board (DSMB)</i> .....	68
6.9.2.1.	Potential Vaccine Harm .....	68
7.	<b>CHANGES FROM PLANNED ANALYSES IN PROTOCOL</b> .....	69
8.	<b>REFERENCES</b> .....	69
9.	<b>LIST OF APPENDICES</b> .....	70
9.1.	APPENDIX A STANDARDS FOR VARIABLE DISPLAY IN TFLs .....	70
9.2.	APPENDIX B ANALYSIS VISIT WINDOWS .....	71
9.3.	APPENDIX C IMPUTATION RULES FOR MISSING DATES OF PRIOR/CONCOMITANT MEDICATIONS AND NON-STUDY VACCINATIONS .....	73
9.4.	APPENDIX D IMPUTATION RULES FOR MISSING DATES OF AEs .....	74
9.5.	APPENDIX E SCHEDULE OF EVENTS .....	75
9.6.	APPENDIX F ESTIMANDS AND ESTIMAND SPECIFICATIONS .....	76

## LIST OF TABLES

Table 1:	Derivation for COVID-19 (primary efficacy endpoint).....	33
Table 2:	Censoring Rules for COVID-19.....	37
Table 3:	Derivation of Secondary efficacy endpoint: Serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.....	43
Table 4:	Interim Boundaries Using O'Brien-Fleming Spending function, Calculation Based on the PP Set for the Primary Efficacy Endpoint .....	48
Table 5:	Burden of Disease Score .....	61
Table 6:	Burden of Infection Score .....	63
Table 7:	Grading of COVID-19 Symptoms .....	64
Table 8:	Analysis Visit Windows.....	71
Table 9:	Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations .....	74
Table 10:	Intercurrent Event Types.....	76
Table 11:	Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for Per Protocol Analysis .....	77

## LIST OF FIGURES

Figure 1:	Study Design Schematic .....	17
Figure 2:	Event/Case-Driven Study with 24 Months of Planned Follow-Up.....	18
Figure 3:	Scheme of Derivation of Secondary Efficacy Endpoint: Serologically Confirmed SARS-CoV-2 Infection or COVID-19 Regardless of Symptomatology or Severity .....	42
Figure 4:	Testing Strategy of Primary and Secondary Efficacy Endpoints.....	51

### 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
cLDA	constrained Longitudinal Data Analysis
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

<b>Abbreviation</b>	<b>Definition</b>
HR	hazard ratio
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
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

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P301, is based on the most recent clinical study protocol (CSP) Amendment 3, dated 20-August-2020. The most recent approved electronic case report form (eCRF) Version 2.026, dated 21-AUG-2020.

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. The SAP will be 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 ( $\geq 38^{\circ}\text{C}$ ), 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.
- Unsolicited adverse events (AEs) through 28 days after each injection of IP.
- Medically-attended AEs (MAAEs) or AEs leading to withdrawal through the entire study period.
- Serious AEs (SAEs) throughout the entire study period.
- Pregnancies and perinatal outcomes.

## 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  $\geq 30$  per minute, Heart Rate  $\geq 125$  beats per minute,  $\text{SpO}_2 \leq 93\%$  on room air at sea level or  $\text{PaO}_2/\text{FIO}_2 < 300$  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, defined as for the primary endpoint, and asymptomatic SARS-CoV-2 infection, assessed by seroconversion and with a negative NP swab sample for SARS-CoV-2 at Day 1
- 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  $\geq 38^\circ\text{C}$ ), 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.
- 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 Phase 3, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 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

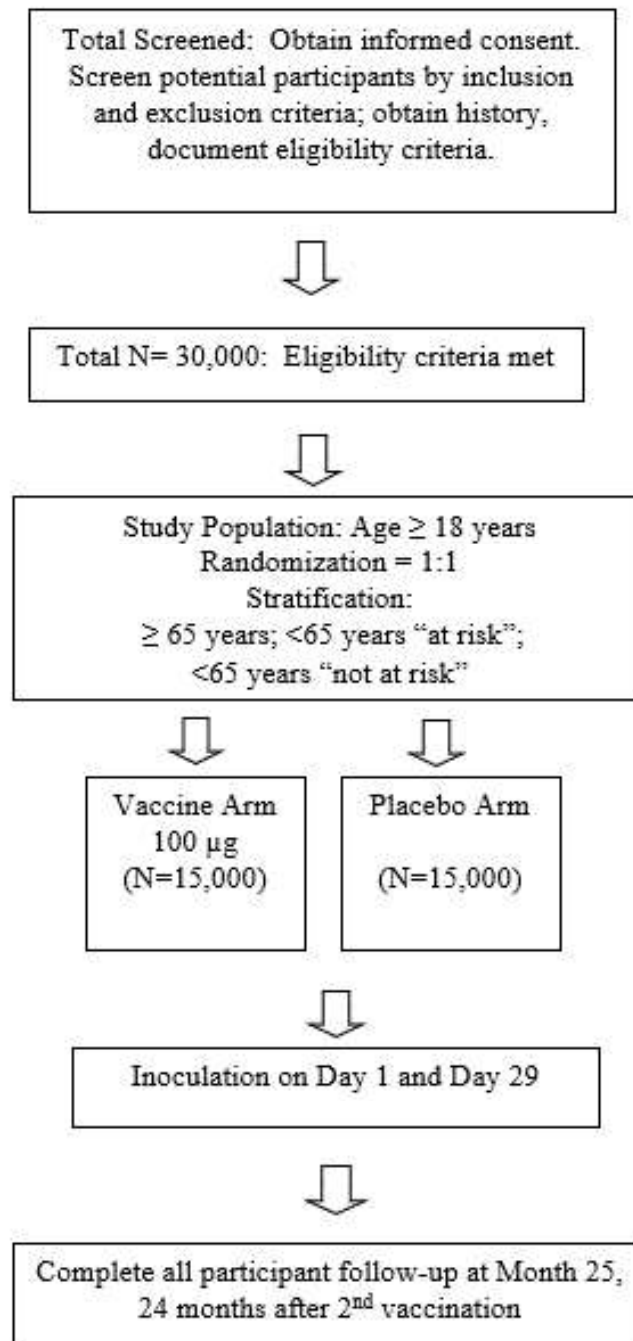
stratified by age and health risk. This is a case-driven study and thus final study size will depend on the actual attack rate of COVID-19.

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. If the pre-specified criteria for early efficacy are met at the time of either interim analysis (IA) or overall efficacy at the primary analysis, an initial study report describing the efficacy and safety of mRNA-1273 will be prepared based on the data available at that time. In the event that success criteria are met either at the time of the interim analyses or when the total number of cases toward the primary endpoint has accrued, subjects will continue to be followed in a blinded fashion until Month 25, to enable assessment of long-term safety and durability of VE ([Figure 2](#)). If the study concludes early, all participants will be requested to provide a final blood sample at the time of study conclusion.

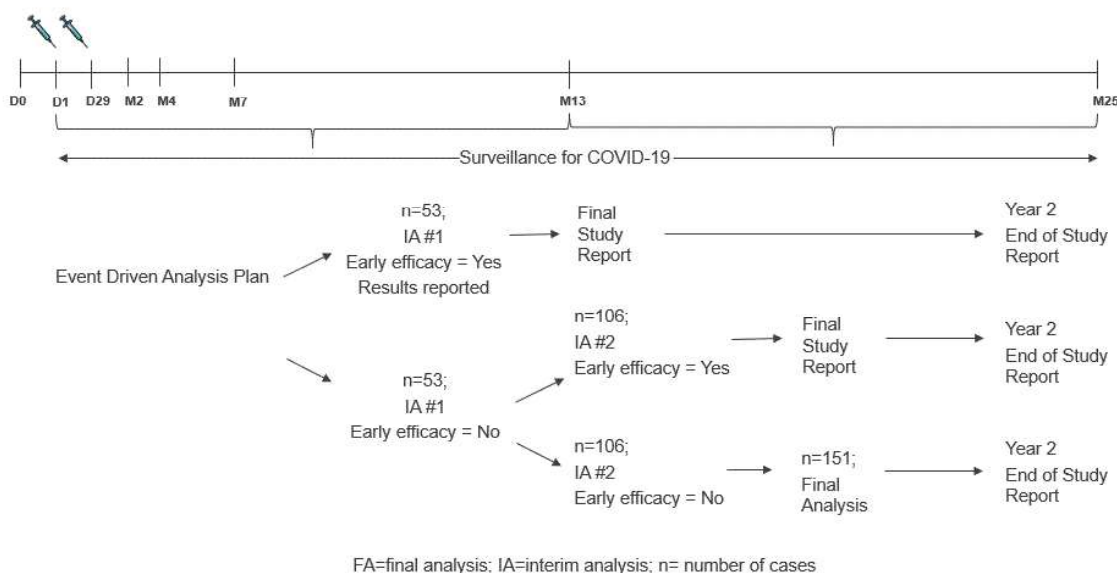
Participants will use an electronic diary (eDiary) to report solicited adverse reactions (ARs) after each injection of IP and to prompt an unscheduled clinic visit if experiencing any symptoms of COVID-19. Surveillance for COVID-19 will be performed through weekly contacts with the participants via a 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 Design Schematic**



**Figure 2: Event/Case-Driven Study with 24 Months of Planned Follow-Up**



## 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  $\leq 30\%$ , i.e.  $H_0^{\text{efficacy}}: \text{VE} \leq 0.3$ .

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  $H_0: \text{VE} \leq 30\%$ , 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 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  $\geq 90\%$  power to demonstrate the VE is above 30% (to reject null hypothesis  $VE \leq 30\%$ ) 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 ( $\geq 18$  and  $< 65$ , or  $\geq 65$  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:

- $\geq 18$  and  $< 65$  years and not at risk
- $\geq 18$  and  $< 65$  years and at risk
- $\geq 65$  years

At least 25% of enrolled participants, but not to exceed 40%, will be from the  $\geq 65$  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 9.5](#) 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.

## **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.

### **5.5. Immunogenicity Subset**

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)]. The ccIAS cohort consists of a stratified random sample of trial participants, 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 (i.e., all subjects in the FAS who had a valid immunogenicity test result) who had a valid baseline immunogenicity test result (prior to the first injection of IP) and at least one valid post-baseline result.

The details of the case-cohort sampling will be included in the Analysis Plan for the Immunogenicity Data.

### **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 14](#) (Vaccination Phase, Day 1 – Day 57), [Table 15](#) (Surveillance Phase, Day 64 – Day 394), [Table 16](#) (Surveillance Phase, Day 401 – Day 759), and [Table 17](#) (Convalescent Period, 28-Day Follow-up starting with the Illness Visit).

**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 status 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 baseline 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. Subjects with positive status at Baseline will be excluded from the mITT and PP population.

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.

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.

**For calculations regarding** antibody values/titers reported as below LOD or LLOQ will be replaced by  $0.5 \times \text{LOD}$  or  $0.5 \times \text{LLOQ}$ . Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

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

- Up to 28 days after any vaccination: this stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.
- Follow-up analysis period:

For unsolicited AE or assessments that will be collected throughout the study, this analysis period starts from 28 days after the last injection date (i.e. the day of last injection + 28 days, regardless of number of injections received) and continues until the earliest date of (study completion, discontinuation from the study, or death).

For assessments that will be collected at study visits (e.g. vital sign), if a subject receives two injections, this stage starts from the day after Day 57 visit and continues until the earliest date of (study completion, discontinuation from the study, or death); if a subject receives first injection only, this stage starts from the day after Day 29 visit and continues until the earliest date of (study completion, discontinuation from the study, or death).

- Overall period: this analysis period starts at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).

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

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

**Visit windowing rules:** The analysis visit windows for protocol-defined visits are provided in [Appendix B](#).

**Incomplete/missing data:**

- Imputation rules for missing 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  $0.5 \times \text{LLOQ}$  in the summary. 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:

- 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/displays for efficacy will be provided by treatment group using appropriate analysis population unless otherwise specified.

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
- Immunogenicity Subset

- 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.  $\geq 18$  and  $< 65$  years and not at risk,  $\geq 18$  and  $< 65$  years and at risk, or  $\geq 65$  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

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

In addition, subjects with any inclusion and exclusion criteria violation will also 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) ( $\text{kg/m}^2$ ). The number and percentage of subjects will be provided for categorical variables such as age group, sex, race, ethnicity, randomization stratum per IRT, 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  $\geq 40 \text{ kg/m}^2$ )
- 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.

For screened failure subjects, age (years), gender, race, and ethnicity will be presented in a listing.

### **6.2.3. Medical History**

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

The number and percentage of participants with any medical history will be summarized by SOC and PT based on Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of 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 9](#).

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

- Any concomitant medications throughout the study
- Any concomitant medications and non-study vaccinations within 7 Days Post Injection
- Any concomitant medications and non-study vaccinations within 28 Days Post Injection
- Seasonal influenza vaccine within 28 Days Post Injection
- Prophylactic antipyretics or analgesics medication within 28 Days Post Injection
- Antipyretic or analgesic medication within 28 Days Post Injection

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

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

#### **6.2.5. Study Exposure**

Study IP administration data will be presented in a listing.

#### **6.2.6. Major Protocol Deviations**

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

The number and percentage of the subjects with each major protocol deviation type will be provided by treatment group as defined in [Section 6.1](#) based on the Randomization Set.

Major protocol deviations will be presented in a listing.

#### **6.2.7. COVID-19 Impact**

A listing will be provided for COVID-19 impact.

### **6.3. Efficacy Analysis**

Efficacy analyses will be performed using the PP Set, mITT Set, and FAS. The PP Set is the primary analysis population used in the efficacy analyses, unless otherwise specified. 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) will review potential cases. The AC will be

blinded to treatment assignment. If the assessments of the AC are available, the primary endpoint and the secondary efficacy endpoints will be based on assessments of the AC.

**Baseline SARS-CoV-2 status** is described in [Section 6.1](#). Baseline SARS-CoV-2 status, the serology test results based on Roche Elecsys assay at Baseline, the RT-PCR test results at baseline on or before Day 1 will be summarized by treatment group.

Participants with baseline positive SARS-CoV-2 status will be excluded from the mITT and PP Sets; participants with baseline positive SARS-CoV-2 status will be included in the FAS and Safety Sets.

In this study, RT-PCR test results will be summarized by visit. Summary tables of the primary and secondary efficacy endpoints will be also provided.

### **6.3.1. Analysis of Primary Efficacy Endpoint**

#### **6.3.1.1. Primary Efficacy Endpoint Definition/Derivation**

The primary efficacy endpoint 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). In this study, there is a scheduled NP swab test at the Day 29 visit prior to the 2<sup>nd</sup> injection of IP, the RT-PCR results from the scheduled NP swab tests at the Day 29 visit prior to the 2<sup>nd</sup> injection of IP will not be considered for derivation of COVID-19 as they are not prompted by symptoms.

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](#).

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

	<b>COVID-19</b>
Post-baseline PCR results at illness visits prompted by symptom(s)  (Scheduled NP swab test at Day 29 visit [2 <sup>nd</sup> injection] will not be used for derivation of efficacy endpoints derivation)	Positive, <b>AND</b>
Systemic Symptoms	at least <b>TWO</b> of the following <b>systemic symptoms</b> : Fever ( $\geq 38^{\circ}\text{C}$ ), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); <b>OR</b>
Respiratory symptoms	at least <b>ONE</b> of the following <b>respiratory</b> 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 systemic symptoms reported, or 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 2<sup>nd</sup> 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 start 14 days after the 2<sup>nd</sup> injection, i.e. date of documented COVID-19 – Date of the 2<sup>nd</sup> injection  $\geq 14$  (starting 14 days after the 2<sup>nd</sup> injection).

In the primary analysis approach for the primary efficacy endpoint, the first occurrence of COVID-19 starting 14 days after the 2<sup>nd</sup> 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.

Please note, subjects with Baseline Positive SARS-CoV-2 status will be excluded from the mITT and PP Set; subjects with Baseline Positive SARS-CoV-2 status will be included in the FAS and Safety Sets.

#### **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  $\geq 14$ ) 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 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). Equivalently, the null hypothesis is:

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

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. The HR with corresponding alpha-adjusted confidence interval (CI), 95% CI, and 2-sided *p*-value for testing the null hypothesis from the stratified Cox model will be reported.

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 cause 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) and subjects who were censored will be reported.

Potential intercurrent events to the estimand are listed in [Appendix F Table 10](#). The primary estimand with rationale for strategies to address intercurrent events is summarized in [Appendix F Table 11](#).

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

Four sets of 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

**Table 2: Censoring Rules for COVID-19**

<b>Situation</b>	<b>Primary Efficacy Approach (cases starting 14 days after the 2<sup>nd</sup> injection)</b>	<b>Sensitivity Analyses</b>			
		<b>Cases starting immediately after the 2<sup>nd</sup> injection</b>	<b>Cases starting 14 days after the 1<sup>st</sup> injection</b>	<b>Cases starting immediately after the 1<sup>st</sup> injection</b>	<b>Cases starting immediately after randomization</b>
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 first injection up to 14 days after first injection	Censored at date of case	Censored at date of case	Censored at date of case	Event	Event
Early case from 14 days after first injection up to second injection	Censored at date of case	Censored at date of case	Event	Event	Event
Early case from second injection up to 14 days after second	Censored at date of case	Event	Event	Event	Event

Situation	Primary Efficacy Approach (cases starting 14 days after the 2 <sup>nd</sup> injection)	Sensitivity Analyses			
		Cases starting immediately after the 2 <sup>nd</sup> injection	Cases starting 14 days after the 1 <sup>st</sup> injection	Cases starting immediately after the 1 <sup>st</sup> injection	Cases starting immediately after randomization
injection					
Early case after 14 days after second injection	Event	Event	Event	Event	Event
Early discontinuation or death without documentation of COVID-19	Censored at date of discontinuation/death				

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 four sets of 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:  $\geq 18$  and  $< 65$  years,  $\geq 65$  years
- Age groups:  $\geq 18$  and  $< 65$  years,  $\geq 65$  years and  $< 75$  years, and,  $\geq 75$  years
- Stratification factor at randomization:  $\geq 18$  and  $< 65$  years and not at risk,  $\geq 18$  and  $< 65$  years at risk,  $\geq 65$  years
- Sex (female, male)
- Race
- Ethnicity
- Each risk factor for severe COVID-19 illness as listed in [Section 6.2.1](#) of the protocol

If the number of subjects in the 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.

#### **6.3.1.5. Supportive Analysis Using Exact Method Based on Incidence Rate**

As a supportive analysis, VE will also be estimated by one minus the ratio of incidence rate (mRNA-1273 vs. placebo), where incidence rate for each treatment group 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 (weeks) in each treatment group. The 95% CI will be computed using the exact method conditional upon the total number of cases.

### **6.3.2. Analysis of 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 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 [-14, +28] days of 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 1<sup>st</sup> occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of randomization +1,

#### **6.3.2.2. Derivation of Secondary Definition of COVID-19**

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

As in the derivation of the primary definition of COVID-19, only RT-PCR tests prompted by symptoms will be considered, i.e. excluding RT-PCR results from the scheduled NP



swab tests at Day 29 prior to the 2<sup>nd</sup> IP dose. 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.

#### **6.3.2.3. 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, 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 2<sup>nd</sup> injection of IP as well as the those prompted by symptom(s). In addition, seroconversion due to infection will also be considered.

The date of documented infection regardless of symptom will be the earlier of:

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

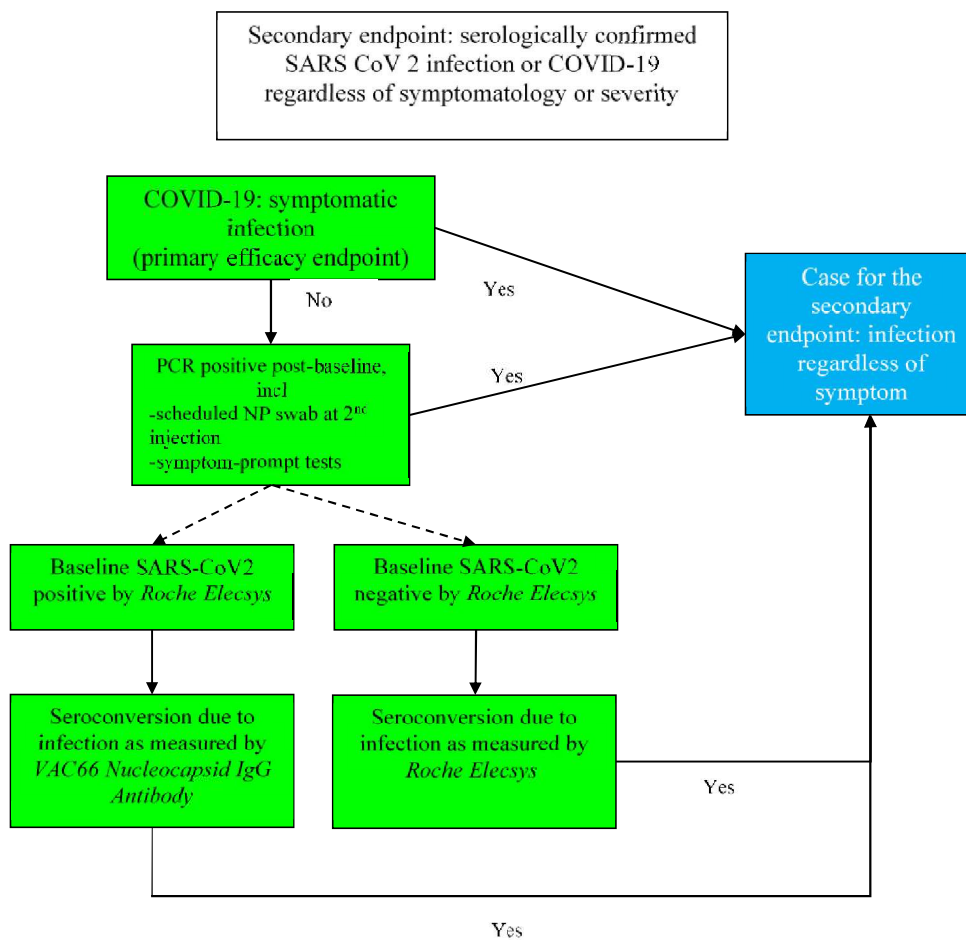
Seroconversion due to infection is defined differently for participants who were seropositive or seronegative at baseline as below:

- Participants seronegative at Baseline (as measured by *Roche Elecsys*): seropositive as measured by *Roche Elecsys* on study
- Participants seropositive at Baseline (as measured by *Roche Elecsys*): 4-fold or more increase in bAb from baseline as measured by *VAC66 Nucleocapsid IgG Antibody* on study

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

Derivation of this secondary efficacy endpoint is summarized in [Figure 3](#) and [Table 3](#).

**Figure 3: Scheme of Derivation of Secondary Efficacy Endpoint: Serologically Confirmed SARS-CoV-2 Infection or COVID-19 Regardless of Symptomatology or Severity**



**Table 3: Derivation of Secondary efficacy endpoint: Serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity**

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	
Negative at Baseline	<b>positive</b> at symptom-prompt NP swab test (Illness visit), or at scheduled D29 NP swab test before 2nd dose	N/A	Case
Negative at Baseline	No positive PCR test	Seroconversion as measured by Roche Elecsys	Case
Positive at Baseline			
PCR positive at baseline		N/A	already had prior infection, not at risk, subjects will NOT be a case, and will be censored at date of randomization
PCR negative at baseline, AND, detectable bAb by Roche Elecsys	PCR positive		Case
PCR negative at baseline, AND, detectable bAb by Roche Elecsys		Seroconversion due to infection, as measured by VAC66 Nucleocapsid IgG Antibody	Case

#### 6.3.2.4. Derivation of Asymptomatic SARS-CoV-2 Infection

SARS-CoV-2 infection is defined by seroconversion due to infection measured by bAb against SARS-CoV-2 nucleocapsid in subjects who had a negative RT-PCR test at baseline. In protocol amendment 2, a Day 29 NP swab prior to Dose 2 is added and thus will be taken into consideration for the efficacy endpoint of SARS-CoV-2 infection. Please note asymptomatic infection is identified by seroconversion only at months 1, 2, 7, 13 and 25, when blood samples for immunogenicity are collected; at month 1 (Day 29), both RT-PCR test and bAb against SARS-CoV-2 nucleocapsid will be considered.

The date of documented asymptomatic infection is the date of seroconversion due to infection, defined as the date of achieving:

- Seropositive as measured by *Roche Elecsys* on study, for participants seronegative at Baseline (as measured by *Roche Elecsys*)
- 4-fold or more increase in bAb from baseline as measured by *VAC66 Nucleocapsid IgG Antibody* on study, for participants seropositive at Baseline (as measured by *Roche Elecsys*)
- Positive RT-PCR at scheduled Day 29 nasal swab test prior to 2<sup>nd</sup> dose

For participants who had a symptomatic infection (e.g., COVID-19 as primary endpoint, or secondary definition of COVID-19), following seroconversion will not be considered for derivation of asymptomatic infection, i.e. participants who had a symptomatic 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 2<sup>nd</sup> IP dose, which requires seroconversion at months 2 (Day 57 visit) or later.

#### 6.3.2.5. Analysis of 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
- VE to prevent asymptomatic SARS-CoV-2 infection

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, 14 days after the first injection of IP, immediately after the first injection of IP, and immediately after randomization respectively.
- VE and 95% CI based on the incidence will be estimated with  $1 - \text{ratio of incidence rates}$  using the exact method conditional upon the total number of cases.

In addition, the following efficacy endpoints will be also analyzed:

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 after the first injection of IP as described in [Section 6.3.1](#).

#### VE to prevent all-cause mortality

This endpoint will be analyzed with the same Cox PH model described above based on the PP Set, mITT Set, and FAS. Death, regardless of cause, from randomization will be included. Time to death will be calculated as date of death – date of randomization + 1. Subjects with no documented death will be censored at the last date of study participation for study completion, early discontinuation, or lost to follow-up.

#### 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 at least 14 days after the second injection of IP. Subjects who received only the first injection of IP will be excluded from the statistical analysis. Sensitivity analyses with cases counted starting immediately after the second injection, 14 days after the first injection, immediately 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 will be excluded from the statistical analysis. The VE will be also estimated with 1- ratio of incidence rates with the 95% CI using the exact method conditional upon the total number of cases.

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 to assess the VE in those with positive baseline SARS-CoV-2 status, at baseline, if sample size permits.

### **6.4. Interim Analyses**

There are two planned interim analyses in this study, which will be performed when approximately 35% and 70% of the target total number of COVID-19 cases across the two vaccine groups have been observed respectively. The primary objective of the IAs is for early detection of reliable evidence that VE is above 30%. The Lan-DeMets O'Brien-Fleming approximation spending function is 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. There is no intention to stop the study early if the efficacy has been demonstrated at any of the IAs. If efficacy is demonstrated at an IA, the subsequent IA or primary analysis will be considered supportive in nature. The IA results will be reviewed by the DSMB.

The first IA will occur when 35% of the total cases in the PP set have been observed. The study will be considered positive at this IA if the  $p$ -value for rejecting  $HR \geq 0.7$  is 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 will 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  $HR \geq 0.7$  is 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 will be performed when approximately 151 cases have been observed in the PP Set. The study will be considered positive at the primary analysis when a total of 151 cases have been observed and if the one-sided  $p$ -value for rejecting  $HR \geq 0.7$  is 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 will carry out the IAs. The unblinded statistics team will 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 will be performed after all subjects have completed the study and after the database is cleaned and locked. Results of this analysis will be presented in a CSR, including individual listings.

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 $\leq$ 30% (HR $\geq$ 0.7)	Cum Prob (crossing efficacy boundary if the true VE = 60%)
IA1 35%	53	0.0002	VE $\geq$ 0.741 (HR $\leq$ 0.259)	4.6%
IA2 70%	106	0.0073	VE $\geq$ 0.565 (HR $\leq$ 0.435)	61.5%
Primary analysis 100%	151	0.0227	VE $\geq$ 0.495 (HR $\leq$ 0.505)	90.0%

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

## 6.5. Multiplicity Adjustments

The overall type I error rate for this study is strictly 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  $\geq 20$  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  $VE \leq 0\%$  null hypothesis. If hypothesis test against  $VE \leq 0\%$  are rejected for all three, sequential testing against a  $VE \leq 10\%$  for these three secondary efficacy endpoints will be performed in the same order; if hypothesis test against  $VE \leq 10\%$  are rejected for all three, sequential testing against a  $VE \leq 20\%$  for these three secondary efficacy endpoints will be performed in the same order; if hypothesis test against  $VE \leq 20\%$  are rejected for all three, sequential testing against a  $VE \leq 30\%$  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.

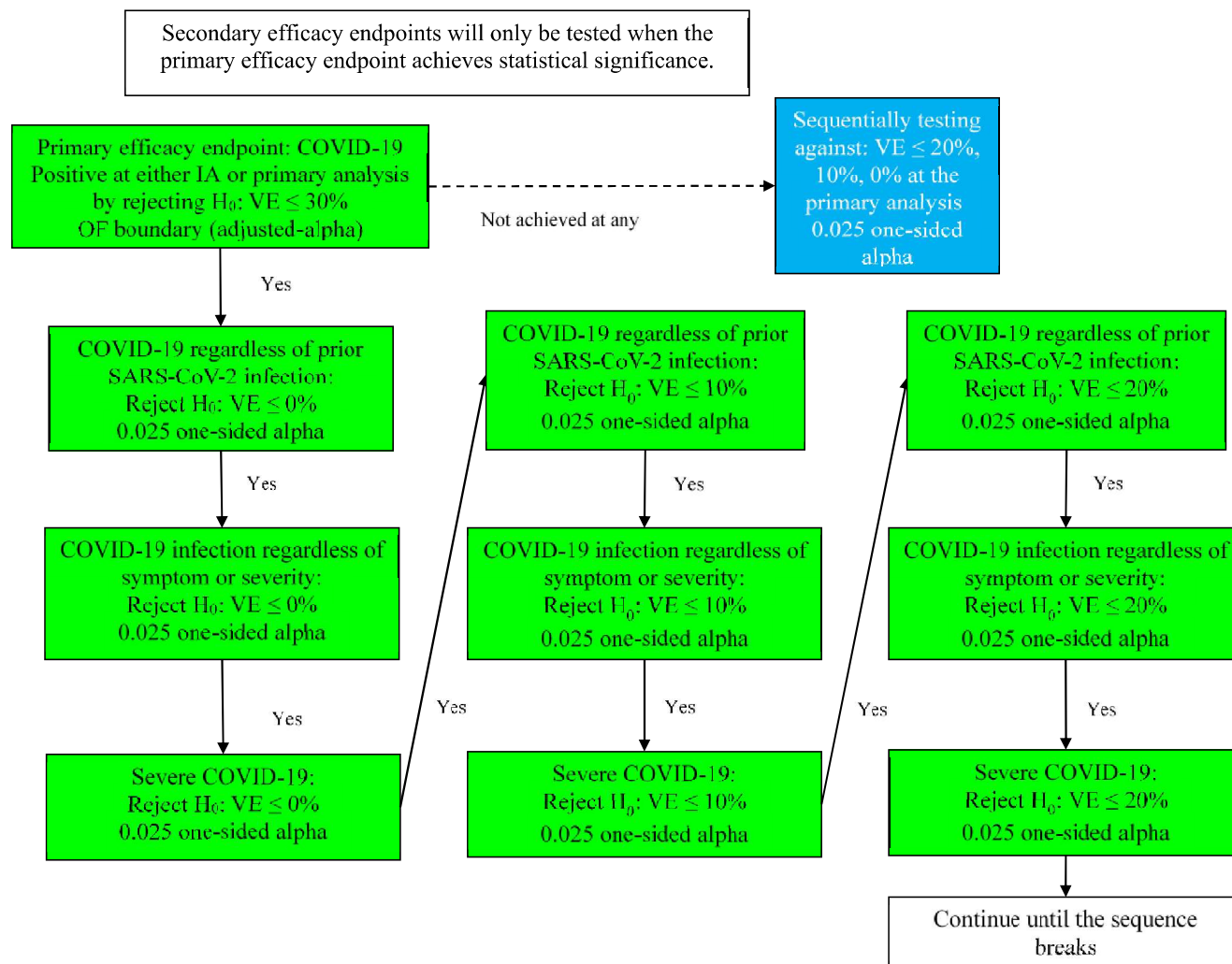
No further testing will be performed once the sequence breaks, that is, further testing stops as soon as an endpoint in the sequence fails to show significance against corresponding null hypothesis regarding VE.

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  $VE \leq 30\%$  null hypothesis at neither the interim analyses nor the primary analysis, at the primary analysis, sequential testing against a  $VE \leq 20\%$ , a  $VE \leq 10\%$ , and a  $VE \leq 0\%$  will be performed, halting when a rejection occurs.

[Figure 4](#) below demonstrates the testing strategy in this study:

**Figure 4: Testing Strategy of Primary and Secondary Efficacy Endpoints**



## 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 5](#) 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.

### 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 Follow-up analysis period, 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.

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 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 TEAEs of Grade 3 or higher
- 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, follow-up analysis period, and for the Overall Stage throughout the study.

In addition, separate listings containing individual subject adverse event data for unsolicited TEAEs, unsolicited treatment-related TEAEs, unsolicited TEAEs leading to

discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, unsolicited TEAEs of Grade 3 or higher, unsolicited treatment-related TEAEs of Grade 3 or higher, serious AEs, serious treatment-related AEs, and unsolicited medically-attended AEs will be provided separately.

#### **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 TEAEs of Grade 3 or higher
- All unsolicited TEAEs of Grade 3 or higher 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 Follow-up analysis period and 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 SOC and PT and 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  $\geq 65$  years)

#### **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 5](#) 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  $\geq$  65 years)

### **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 treatment group as defined in [Section 6.1](#). Shift from baseline in the toxicity grades will also be summarized at each visit by treatment group.

### **6.7. Immunogenicity Analysis**

Immunogenicity Analysis will be based on the Immunogenicity Subset ([Section 5.5](#)). A standalone Analysis Plan for immunogenicity data will describe the details of the case-cohort sampling of the Subset, and analyses of exploratory objectives on immunogenicity including correlates of risk and protection. Analyses of immunogenicity will not be performed at the interim analyses, but at the Primary analysis.

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.

#### **6.7.1. Immunogenicity Data**

Below are the immunogenicity assessments included 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), including tests such as VAC58 Spike IgM Antibody, VAC58 Spike IgA Antibody, and VAC65 Spike IgG Antibody
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays, including tests such as PsVNT50, PsVNT80, and MN50 (live virus neutralization assay)

#### **6.7.2. 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 at each timepoint that an assessment is performed.

- 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.

- The number and percentage of subjects with fold-rise  $\geq 2$ , fold-rise  $\geq 3$ , and fold-rise  $\geq 4$  from Baseline at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs.
- 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 is defined as a change from below the LOD or LLOQ to equal to or above LOD or LLOQ, or at least 4-fold rise if baseline is equal to or above LOD or LLOQ in terms of bAb specific to vaccine antigen (i.e. S protein) or nAb.

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

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

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

where  $t_1, t_2, \dots, t_n$  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:

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

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

where, for  $n$  subjects,  $v_{ij}$  and  $v_{ik}$  are observed immunogenicity titers or levels for subject  $i$  at time points  $j$  and  $k, j \neq k$ .

### 6.7.3. 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 at baseline based on corresponding nAb or bAb respectively. The model will include all available log-transformed anti-body titers at each 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, baseline log-transformed anti-body titers if applicable, and subject as a random effect. 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. In addition, the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference (mRNA-1273 vs. Placebo) at each 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.

In addition, an analysis of covariance (ANCOVA) model with the treatment group and baseline values 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.

## 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 [Table 5](#).

**Table 5: Burden of Disease Score**

<b>Subject State (Worst Category Following Disease Detection)</b>	<b>BOD Score</b>
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 will be performed to compare mRNA-1273 vs. placebo group.

BOD score will be summarized by periods of follow-up time, subjects who are un-diseased at the beginning of each period will be included in the summary for the corresponding period. There will be 4 periods: from randomization through 6 months; 6 months through 12 months; 12 months through 18 months; and 18 months through completion. To assess impact of baseline risk of severe disease on the vaccine effect regarding disease severity, summary of BOD will be provided by randomization strata (i.e.  $\geq 65$  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 will 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 calculated as 1 minus the ratio of means as estimated by a weighted Cox 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 [Table 6](#) and used to understand the impact. Because asymptomatic infection is identified by seroconversion only at months 1, 2, 7, 13 and 25, summary of BOI will be provided for relevant periods (i.e. 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. A t-test of the BOI scores will 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 calculated as 1 minus the ratio of mean BOI scores and reported with 95% confidence intervals. Similarly, in order to assess the infection/disease burden in subjects with infection regardless of symptoms, the above analyses will also be performed in participants with infection regardless of symptoms, i.e. subjects with BOI score of zero will be excluded from such analysis.

**Table 6: Burden of Infection Score**

<b>Patient State (Worst Category Following Disease Detection)</b>	<b>BOI Score</b>
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  $\geq 38^{\circ}\text{C}$ ), 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 [Table 7](#). 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. A subject will have an aggregation score of 0 if never diagnosed with COVID-19. The VE of mRNA-1273 based on mean score of each treatment group will be calculated as below:

$$\text{VE} = [1 - \text{Mean score of mRNA-1273 group} / \text{Mean score of placebo group}] \times 100\%$$

**Table 7: 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	I could not eat or	I have no taste or	3



	able to do activities that I usually do.	drink.	smell.	
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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.

#### **6.8.4. Vaccine Efficacy Against COVID-19 Over Time Based on Instantaneous Hazard Ratio**

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. If the number of severe COVID-19 events (secondary efficacy endpoint) becomes large enough to warrant analysis (upon DSMB recommendation), the same analysis may be applied for this endpoint.

#### **6.8.5. Durability of Vaccine Efficacy Against COVID-19 Using Covariate Adjustment Method Based on Cumulative Incidence**

As an exploratory analysis to assess durability of VE against the primary endpoint, 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 subject 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  $H_0: VE \leq 30\%$  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  $\ell$ , let  $f_{\hat{\alpha}}(\ell)$  denote the  $j \in 1, \dots, 4$  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 Review 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 (current version: Version 1.0)

### **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**

Potential vaccine harm will be assessed based on imbalance between mRNA-1273 vs. placebo for both COVID-19 and severe COVID-19 case counts using the Safety Set.

Subjects will be analyzed according to the IP that they actually received regardless of the group to which they were randomized. For harm monitoring, cases will be counted starting after the first dose of study vaccination. Potential harm will be continuously monitored by DSMB with each case of COVID-19 and severe COVID-19.

Cases of COVID-19 for the harm monitoring are defined as for the primary efficacy endpoint but are based on the Safety Set rather than the PPS.

Details of harm monitoring are provided in the analysis plan for DSMB.

## **7. Changes from Planned Analyses in Protocol**

Not applicable.

## **8. References**

Andersen, P.K., Borgan, O., Gill, R.D., Keiding, N. Statistical Models Based on Counting Processes. Springer. 1993.

Estimands and Sensitivity Analysis in Clinical Trials. To The Guideline on Statistical Principles for Clinical Trials. International Council for Harmonisation (ICH) E9(R1). November 2019.

Gilbert, P.B., Wei, L. J., Kosorok, M. R., Clemens, J. D. Simultaneous Inferences on the Contrast of Two Hazard Functions with Censored Observations. Biometrics. 2002 Dec; 58(4): 773-80.

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U. S. Department of Health and Human Services (DHHS). Food and Drug Administration. Center for Biologics Evaluation and Research. September 2007.

Zeng D. Estimating marginal survival function by adjusting for dependent censoring using many covariates. The Annals of Statistics. 2004, 32(4), 1533-1555.

## 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 8](#) 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 8: Analysis Visit Windows**

Visit	Target Study Day	Visit Window in Study Day
<b>Nasopharyngeal swab (or saliva)</b>		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 29		
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]
<b>Vital Signs</b>		
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, 88]
Day 119	119	[89, 164]
Day 209	209	[165, 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]
<b>Immunogenicity</b>		
Day 1	1	1, Pre-first-dose
Day 29	29 (Date of Second Injection)	[23, 36] 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 [Table 9](#) below.

**Table 9: Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations**

	Medication Stop Date		
	< First Injection Date of IP	$\geq$ First Injection Date and $\leq$ 28 Days After Last Injection	> 28 Days After Last Injection [2]
Medication Start Date			
< First injection date of IP [1]	P	P, C	P, C, A
$\geq$ First injection date and $\leq$ 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 14](#), [Table 15](#), [Table 16](#), and [Table 17](#) in [Appendix 1 Schedule of Events](#) in the protocol.

## 9.6. Appendix F Estimands and Estimand Specifications

**Table 10: Intercurrent Event Types**

Label	Intercurrent Event Type	Comment
IcEv1 (death without confirmation of cases, i.e., unrelated death)	Unrelated death without documented confirmed COVID-19	Participants who die due to reasons unrelated to COVID-19 without confirmation of being a case will all be included in statistical analysis.
IcEv2 (early infection)	Infection starting up to 14 days after the second dose of IP	Participants who experience an early infection up to 14 days after the second dose of IP will all be included in statistical analysis.
IcEv3 (missing dose of IP)	Not receiving the second dose of IP per protocol schedule	Participants who miss a dose of IP will be excluded from the PP, but in the FAS and the mITT.
IcEv4 (SARS-CoV-2 positive at baseline)	Participants with SARS-CoV-2 positive status at baseline	Participants who were SARS-CoV-2 positive at baseline will be excluded from the PP and the mITT but included in the FAS.

10. Abbreviation: IcEv: intercurrent event, PP: per protocol, FAS: full analysis set, mITT: modified intent-to-treat.

**Table 11: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for Per Protocol Analysis**

<b>Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19</b>	
<b>Estimand Description</b>	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 while alive strategy will be used for deaths unrelated to COVID-19, and a treatment policy strategy for early infection. A principal stratum strategy is used to exclude participants missing a dose of IP or being SARS-CoV-2 positive at baseline.
<b>Target Population</b>	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 SARS-CoV-2 pre-positive.
<b>Variable/Endpoint</b>	Time to COVID-19 Disease, censoring at early discontinuation, early infection, or last assessment for an event not being observed, whichever comes earlier.
<b>Treatment Condition(s)</b>	<b>Test:</b> mRNA-1273 <b>Reference:</b> Placebo
<b>Estimand Label</b>	<b>Estimand 1</b>
<b>Population-Level Summary</b>	Vaccine efficacy defined as 1 - HR of mRNA-1273/Placebo
<b>Intercurrent Event Strategy</b>	
<b>IcEv1 (unrelated death):</b>	While alive
<b>IcEv2 (early infection):</b>	Treatment policy
<b>IcEv3 (Missed dose of IP):</b>	Principal stratum

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

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**IcEv4 (SARS-CoV-2  
positive at baseline):**

Principal stratum

N/A

N/A

**Rationale for  
Strategy(s)**

While alive: unrelated death without confirmation of COVID-19 will be censored at the time of death.  
Treatment policy: early case will be censored at the time of confirmation.  
Principal stratum: Participants who were SARS-CoV-2 positive at baseline or missed dose of IP are excluded from this Estimand.

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