ModernaTX, Inc.

Protocol mRNA-1273-P305

A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine

Statistical Analysis Plan

Version 5.0

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
FAS	full analysis set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
IP	investigational product
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAEs	medically attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed effect model repeated measure
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NP	nasopharyngeal
PP	per-protocol
PPSE	per protocol set for efficacy
PPSI	per protocol set for immunogenicity
PPSI-Neg	per protocol set for immunogenicity–SARS-CoV-2 negative

Abbreviation	Definition
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
S	spike
SAE	serious adverse event
SAP	statistical analysis plan
SAR	solicited adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoE	schedule of events
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
VOC	Variants of Concern
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) version 5.0 is based on the clinical study protocol (CSP) Amendment 2, dated 26-August-2022, and electronic case report form (eCRF) Version 5443, dated 14-October-2022. The primary purpose of this SAP amendment is to include more information about the random sample of participants for the exploratory analysis for BA.4/BA.5 variant strain.

Table 1 Summary of Major Changes in SAP, Version 5.0

Section	Brief Description of Changes	Rationale
6.4.1	Included more information about the random sample of participants for the exploratory analysis for BA.4/BA.5 variant strain	Analysis clarification
6.4.2.1.3, 6.4.2.2.3	Added details for the exploratory analysis for BA.4/BA.5 variant strain	Analysis clarification

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9) which provides details on the main study analyses, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

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

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; baseline and pre-booster are used interchangeably.

2. Study Objectives

This study consists of two parts: Part 1 and Part 2 with 2 phases each. Objectives for each study part are the following.

2.1. Primary Objectives

2.1.1. Primary Immunogenicity Objective

Part 1

- To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3.

Part 2

- To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3.
- To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the prototype strain at Day 29 or Month 3.
- To demonstrate superiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3.

2.1.2. Primary Safety Objective

Part 1

- To evaluate the safety and reactogenicity of mRNA-1273.529 and mRNA-1273 administered as a booster dose.

Part 2

- To evaluate the safety and reactogenicity of mRNA-1273.214 and mRNA-1273 administered as a booster dose.

2.2. Secondary Objectives

2.2.1. Secondary Immunogenicity Objectives

Part 1

The key secondary immunogenicity objective is:

- To demonstrate superiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3.

Other secondary objectives are:

- To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against both the B.1.1.529 and the prototype strain at all measured time points.
- To evaluate the seroresponse rate (SRR) of mRNA-1273.529 and mRNA-1273 boosters administered as a 4th dose.

Part 2

- To evaluate the SRR of mRNA-1273.214 and mRNA-1273 boosters administered as a 4th dose.
- To evaluate the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against other variant strains at Day 29 or Month 3.
- To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.214 booster or mRNA-1273 booster.

2.3. Exploratory Objectives

The exploratory objectives are:

Part 1

- To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.529 booster or mRNA-1273 booster.
- To evaluate the immunogenicity of mRNA-1273.529 booster against other variant strains.
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.

Part 2

- To evaluate cellular immunogenicity in a subset of participants.
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.

- To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a 4th dose study vaccine in participants at Month 6.

3. Study Endpoints

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

The primary immunogenicity objectives will be evaluated by the following endpoints:

Part 1

- Geometric mean titer (GMT) of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration.
- Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration.

Part 2

- GMT of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration.
- Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration.
- GMT of mRNA-1273.214 and mRNA-1273 against the prototype strain at Day 29 or Month 3 after study vaccine administration.
- Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Day 29 or Month 3 after study vaccine administration.

3.1.2. Primary Safety Endpoints

The primary safety objectives will be evaluated by the following endpoints in Part 1 and Part 2:

- Solicited local and systemic reactogenicity adverse reactions (ARs) during a 7-day follow-up period after vaccination.
- Unsolicited adverse events (AEs) through the 28-day follow-up period after vaccination.

- Serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (AESIs) from Day 1 to end of study.

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

Part 1

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

- GMT of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration as a 4th dose.
- Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration as a 4th dose.

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

- GMT of mRNA-1273.529 and mRNA-1273 against both the B.1.1.529 and the prototype strain at all measured time points after study vaccine administration as a 4th dose.
- Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against both the B.1.1.529 and the prototype strain at all measured time points after study vaccine administration as a 4th dose.
- SRR against the B.1.1.529 strain as a 4th dose.
- SRR against the prototype strain as a 4th dose.

Part 2

- SRR against the B.1.1.529 strain for boosters administered as a 4th dose.
- SRR against the prototype strain for boosters administered as a 4th dose.
- GMT of mRNA-1273.214 and mRNA-1273 against other variant strains at Day 29 or Month 3 for boosters administered as a 4th dose
- Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against other variant strains at Day 29 or Month 3 for boosters administered as a 4th dose
- SRR against other variant strains for boosters administered as a 4th dose.

- Reverse transcriptase polymerase-chain reaction (RT-PCR)-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants based on the following criteria:
    - Primary case definition
        - The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
        - The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
        - The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
    - Secondary case definition based on the Center for Disease Control and Prevention (CDC) criteria: the presence of one of the CDC listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample.
    - Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment.

3.3. Exploratory Endpoints

The exploratory endpoints of the study are described below.

Part 1

- The criteria of RT-PCR-confirmed symptomatic or asymptomatic SARS-CoV-2 infection definition are the same as described above for **Part 2**.
- GMT of mRNA-1273.529 against other variant strains (e.g., Alpha, Beta, Delta) after study vaccine administration.
- Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against other variant strains after study vaccine administration.

- GMFR of mRNA-1273.529 against other variant strains after study vaccine administration.
- SRR against other variant strains.
- Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence.
- Characterize the immune responses to vaccine breakthrough isolates.

Part 2

- Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of T-cells and B-cells after vaccination.
- Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence.
- Characterize the immune responses to vaccine breakthrough isolates.
- GMT of mRNA-1273.214 against both the B.1.1.529 and the prototype strain at Month 6 after study vaccine administration
- Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Month 6 after study vaccine administration
- Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Month 6 after study vaccine administration
- GMFR of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 and prototype strain at all measured timepoints after study vaccine administration
- SRR against both the B.1.1.529 and prototype strain at Month 6

4. Study Design

4.1. Overall Study Design

The study is a Phase 2/3, two-part, randomized, observer-blind, active-controlled, multicenter study to evaluate the immunogenicity and safety of mRNA-1273.529 and mRNA-1273.214 booster vaccine in medically stable individuals 16 years and older. The

mRNA-1273.529 vaccine contains mRNAs encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). The mRNA-1273.214 vaccine contains mRNAs encoding for both the S-2P of the SARS-CoV-2 Wuhan Hu-1 strain and the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529), formulated in the same LNP.

The study consists of 2 parts with 2 phases each:

In **Part 1**, approximately 600-1000 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.529 or 50 µg of mRNA-1273 (active control). Randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least 90% of participants will receive the study vaccine as the 4th dose.

In **Part 2**, approximately 2,924 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.214 or 50 µg of mRNA-1273 (active control). Randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least 90% of participants will receive study vaccine as the 4th dose.

Each part has a Phase A (randomized, blinded) and Phase B (open-label, observational). Phase B was designed to offer eligible participants in either treatment arms in Part 1 the option to obtain an additional booster after their Month 6 assessment and eligible participants in either treatment arm in Part 2 the option to obtain an additional booster after their Month 3 assessment. The additional booster will be obtained outside of the study.

The potential number of participants in each arm and the randomization ratio can be found in Table 2. The study schema is shown in Figure 1.

Table 2 Study Arm and Dose Levels

Part 1

Vaccination Group	Vaccination Received	Total Dose	N (total)	Study vaccine as the 3rd dose	Study vaccine as the 4th dose
1	mRNA-1273.529	50 µg	300- 500[a]	30-50	270-450
2	mRNA-1273 (Active Control)	50 µg	300- 500[a]	30-50	270-450

Abbreviations: mRNA = messenger ribonucleic acid; N = number.

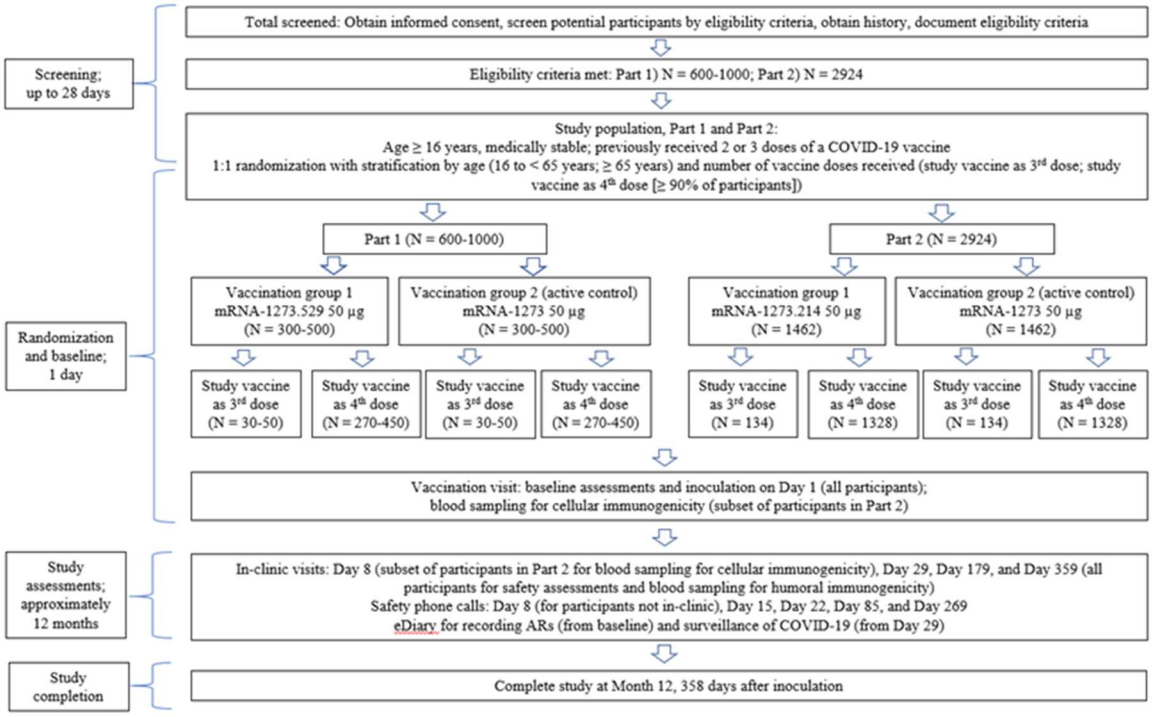
[a] Part 1 will end enrollment when Part 2 starts enrollment. The number of participants in Part 1 will be determined by the start date of Part 2.

Part 2

Vaccination Group	Vaccination Received	Total Dose	N (total)	Study vaccine as the 3rd dose	Study vaccine as the 4th dose
1	mRNA-1273.214	50 µg	1462	134	1328
2	mRNA-1273 (Active Control)	50 µg	1462	134	1328

Abbreviations: mRNA = messenger ribonucleic acid; N = number.

Figure 1 Study Schema



All participants will have previously received 2 or 3 doses of an authorized/approved COVID-19 vaccine. Participants who had previously received 2 doses of a COVID-19 vaccine as a primary series will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the 3rd dose, and participants who have previously received a primary series and one booster dose will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the 4th dose. Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine as the 3rd dose of a COVID-19 vaccine. Participants who will

receive the 3rd dose as part of the study may have previously received 2 doses of a mRNA or a non-mRNA COVID-19 vaccine (a mixed approach is acceptable).

Except for appropriately delegated unblinded pharmacists, vaccine administrators and monitors, all personnel involved in the conduct of the study will remain blinded to individual treatment assignment until study unblinding. Study visits will consist of a Screening Visit (up to 28 days before the Day 1 visit), Vaccination Visit at Day 1 and subsequent study visits on Day 8 (for a subset of participants in Part 2 of the study), Day 29 (Month 1), Day 85 (Month 3), Day 179 (Month 6), and Day 359 (Month 12), with up to 13 months of study participation. Unscheduled visits for potential symptoms of COVID-19 will include PCR testing. The Schedule of Events (SoE) is provided in Appendix E.

4.2. Statistical Hypotheses

Part 1

The primary study objective on immune response in Part 1 is based on the participants who will receive the 4th dose in Part 1 of the study.

Primary Hypotheses:

1) mRNA-1273.529, as a single booster dose, is non-inferior to mRNA-1273 based on GMR against the B.1.1.529 strain with a non-inferiority margin of 1.5 at Day 29.
2) mRNA-1273.529, as a single booster dose, is non-inferior to mRNA-1273 based on GMR against the B.1.1.529 strain with a non-inferiority margin of 1.5 at Month 3.

Key Secondary Hypothesis:

mRNA-1273.529, as a single booster dose, is superior to mRNA-1273 based on GMR against the B.1.1.529 strain at Day 29 or Month 3.

For the primary objective of immune response, hypotheses testing based on participants receiving the 4th dose, alpha of 0.05 (two-sided) will be allocated between the two time points. Alpha of 0.01 (two-sided) will be allocated to Day 29 and alpha of 0.04 (two-sided) will be allocated to Month 3.

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Day 29 will be assessed using a non-inferiority margin of 1.5 at two-sided alpha of 0.01. The primary immunogenicity objective is considered met if non-inferiority against the

B.1.1.529 strain is demonstrated, i.e., the lower bound of the 99% confidence interval (CI) of the GMR of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5).

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Month 3 will be assessed using a non-inferiority margin of 1.5 at two-sided alpha of 0.04. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain is demonstrated, i.e., the lower bound of the 96% confidence interval (CI) of the GMR of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5).

Part 2

The primary objective on immune response in Part 2 is based on the participants who will receive the 4th dose in Part 2 of the study. There are six hypotheses on immune response of mRNA-1273.214 listed below. Part 2 of this study is considered to have met its primary objective if non-inferiority of mRNA-1273.214 against the B.1.1.529 strain, non-inferiority of mRNA-1273.214 against the prototype strain, and superiority of mRNA-1273.214 against the B.1.1.529 strain are demonstrated as compared to mRNA-1273 at Day 29 or Month 3.

Figure 2 details the hypotheses testing strategy specific to Part 2.

Primary Hypotheses:

1) mRNA-1273.214, as a single booster dose, is non-inferior to mRNA-1273 based on GMR against the B.1.1.529 strain with a non-inferiority margin of 1.5 at Day 29.
2) mRNA-1273.214, as a single booster dose, is non-inferior to mRNA-1273 based on GMR against the prototype strain with a non-inferiority margin of 1.5 at Day 29.
3) mRNA-1273.214, as a single booster dose, is superior to mRNA-1273 based on GMR against the B.1.1.529 strain at Day 29.
4) mRNA-1273.214, as a single booster dose, is non-inferior to mRNA-1273 based on GMR against the B.1.1.529 strain with a non-inferiority margin of 1.5 at Month 3.
5) mRNA 1273.214, as a single booster dose, is non-inferior to mRNA -1273 based on GMR against the prototype strain with a non-inferiority margin of 1.5 at Month 3.
6) mRNA-1273.214, as a single booster dose, is superior to mRNA-1273 based on GMR against the B.1.1.529 strain at Month 3.

For the primary objective of immune response, hypotheses testing based on participants receiving the 4th dose, alpha of 0.05 (two-sided) will be allocated to the two time points: alpha of 0.01 (two-sided) will be allocated to Day 29, and alpha of 0.04 (two-sided) will be allocated to Month 3.

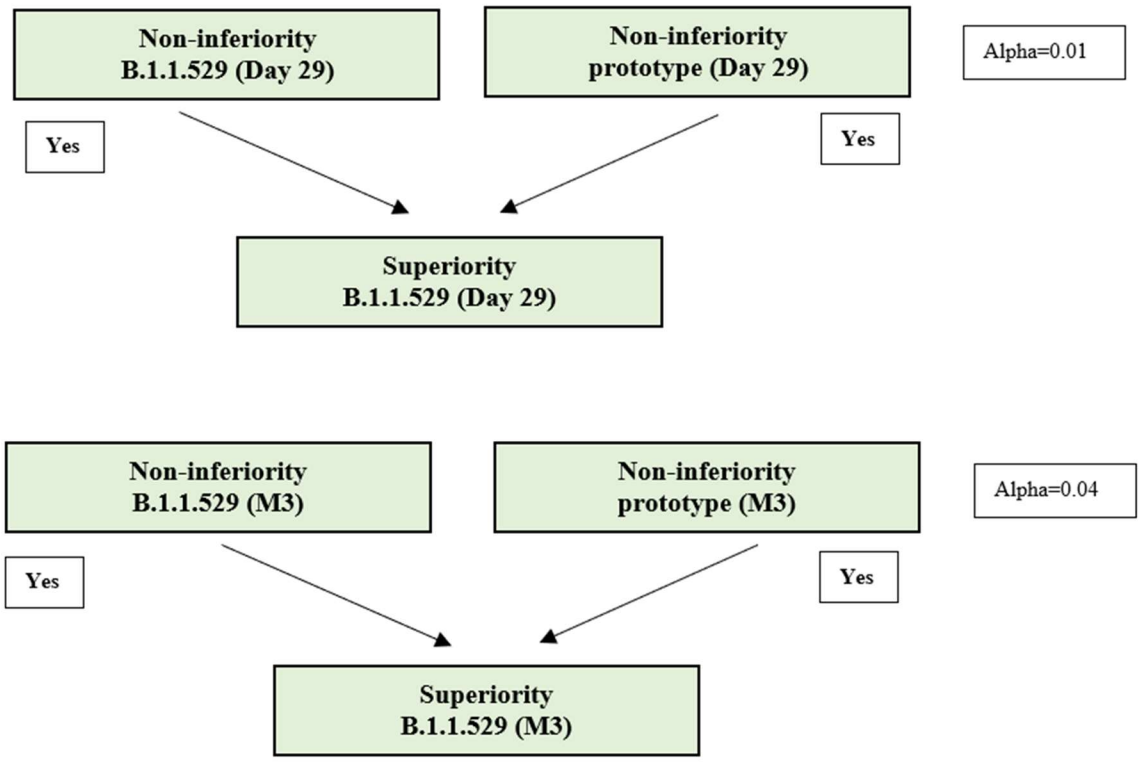
For the primary immunogenicity objective, the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain and the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the prototype strain at Day 29 will be assessed using a non-inferiority margin of 1.5 at two-sided alpha of 0.01. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain and the prototype strain are both demonstrated, i.e., the lower bound of the 99% confidence interval (CI) of the GMR of mRNA-1273.214 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5) and the lower bound of the 99% CI of the GMR of mRNA-1273.214 vs mRNA-1273 against prototype is ≥ 0.67.

Superiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain will be evaluated at Day 29. Once the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain and against the prototype strain is demonstrated, the 99% CI of GMR (mRNA-1273.214 vs. mRNA-1273) will be used to assess superiority

of mRNA-1273.214 as compared to mRNA-1273. If the lower bound of the GMR rules out (>) 1 at Day 29, superiority of mRNA-1273.214 compared to mRNA-1273 against B.1.1.529 will be considered demonstrated.

Hypotheses testing at Month 3 will be performed in the same manner, first testing two non-inferiority hypotheses (one against the B.1.1.529 strain and one against the prototype strain) at alpha of 0.04 level (two-sided). Once non-inferiority is demonstrated for both B.1.1.529 and prototype strains, then superiority testing against the B.1.1.529 at alpha of 0.04 level (two-sided) will be performed.

Figure 2 Statistical hypothesis testing strategy of mRNA-1273.214 vs. mRNA-1273 (Part 2)



Abbreviations: M = month; mRNA = messenger ribonucleic acid.

4.3. Sample Size and Power

Two groups of participants will be included in this study:

1. Participants who received two doses of a COVID-19 vaccine as the primary series and the 3rd dose of a COVID-19 vaccine and will receive the 4th dose as part of the study.
2. Participants who received two doses of a COVID-19 vaccine as the primary series and will receive the 3rd dose as part of the study.

Part 1 (50 µg mRNA-1273.529 and 50 µg mRNA-1273 in 1:1 ratio)

The primary immunogenicity objective is to assess immune response of mRNA-1273.529 against B.1.1.529 strain in participants who are receiving mRNA-1273.529 (or mRNA-1273) as the 4th dose in Part 1 of this study.

The target enrollment is approximately 500 participants (minimum 300 participants) in each treatment arm (1:1). The assumptions are: 1) at least CCI participants will be in 4th dose subgroup; and 2) CCI of participants will be excluded from the Per-Protocol (PP) Set for immunogenicity, SARS-CoV-2 negative (e.g., due to infection with the SARS-CoV-2 Omicron variant).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, two-sided):

With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at two-sided alpha of 1.0% at Day 29. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a two-sided alpha of 1% at Day 29 ranges from CCI. The assumptions are: the true GMR (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

Statistical power for hypotheses testing at Month 3 (alpha=0.04, two-sided):

With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at two-sided alpha of 4% at Month 3. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a two-sided alpha of 4% at Month 3 ranges from CCI. The assumptions are: the true GMR (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5. Specific operating characteristics for Part 1 are provided in Table 3. With approximately CCI participants receiving the 4th dose in each study arm, there is at least 90% probability to observe one participant reporting an AE in each study arm if the true incidence of AEs is 1%.

Table 3 Operating Characteristics and Power for the Primary and Key Secondary Objectives Under Various GMRs and the Number of Evaluable Participants with Immunogenicity Data Who Receives the 4th Dose in this Study (Part 1)

True GMR (mRNA-1273.529 vs. mRNA-1273 against B.1.1.529)	Number evaluable patients per arm (4^{th} dose)	Minimum empirical GMR for the primary objective	Power
Two-sided Type I Error (α) = 0.01 (Day 29)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
Key Secondary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			
Two-sided Type I Error (α) = 0.04 (Month 3)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
Key Secondary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			

CCI			

Abbreviations: GMR = geometric mean titer ratio; mRNA = messenger ribonucleic acid.

Part 2 (50 µg mRNA-1273.214 and 50 µg mRNA-1273 in 1:1 ratio)

The primary immunogenicity objective is to assess immune response of mRNA-1273.214 against B.1.1.529 and prototype in participants who are receiving mRNA-1273.214 (or mRNA-1273) as the 4th dose in Part 2 of this study. The sample size is driven by this subgroup.

Hypotheses testing on immunogenicity data will be performed at two time points: Day 29, and Month 3 post-booster. To preserve family-wise alpha of 0.05 (two-sided), alpha will be allocated to Day 29 of 0.01 (two-sided), and Month 3 of 0.04 (two-sided).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, two-sided):

For the 4th dose subgroup, the target enrollment is approximately 1328 participants in each treatment arm (1:1). Assuming CCI of participants will be excluded from the PP Set for Immunogenicity, SARS-CoV-2 negative, with approximately CCI evaluable participants in each arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 against the B.1.1.529 and against the prototype at two-sided alpha of 1.0%. With this sample size, there is approximately CCI power to demonstrate superiority of mRNA-1273.214 against the B.1.1.529 variant strain at a two-sided alpha of 1.0% at Day 29. The assumptions are: the true GMR (mRNA-1273.214 vs. mRNA-1273) against the B.1.1.529 strain ranges from CCI and the true GMR (mRNA-1273.214 vs. mRNA-1273) against the prototype strain is [redacted], the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

Statistical power for hypotheses testing at Month 3 (alpha=0.04, two-sided):

With approximately CCI evaluable participants in each arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 against the B.1.1.529 and against prototype at two-sided alpha of 4%. With this sample size, there is approximately CCI [redacted] power to demonstrate superiority of mRNA-1273.214 against the B.1.1.529 strain at a two-sided alpha of 4% at Month 3. The assumptions are: the true GMR (mRNA-1273.214

vs. mRNA-1273) against the B.1.1.529 strain ranges from CCI and the true GMR (mRNA-1273.214 vs. mRNA-1273) against the prototype strain is [redacted], the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

With approximately 1328 participants receiving the 4th dose in each study arm, there is at least 90% probability to observe one participant reporting an AE in each study arm if the true incidence of AEs is 1%.

The enrollment target of this study is approximately 1328 participants per arm to receive the 4th dose. The Omicron variant of concern (VOC) has spread quickly throughout the world. There may be an urgency to perform Day 29 or Month 3 analysis as early as possible, and depending on the operational feasibility, particularly the testing capability of assays of antibodies against B.1.1.529, the Sponsor may decide to perform the analysis of immunogenicity after immunogenicity data from a subset of the participants receiving the 4th dose becomes available. Such a decision will be documented prior to the planned analysis at Day 29 or Month 3.

Table 4 includes the power and operating characteristics under various GMRs and two different scenarios for the number of evaluable participants with immunogenicity data. Based on CCI evaluable participants per arm (4th dose), under the same assumptions outlined above, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 compared to mRNA-1273 against B.1.1.529 at Day 29 at $\alpha = 1\%$ if true GMR CCI; and there is approximately CCI power to demonstrate superiority at $\alpha = 1\%$ if the true ratio if CCI. With this size, there is CCI power at Month 3 (primary objective) at $\alpha = 4\%$ (two-sided) if the true GMR is CCI and there is CCI power to demonstrate superiority at $\alpha = 4\%$ (two-sided) if the true GMR is CCI.

Table 4 Operating Characteristics and Power for the Primary and Key Secondary Objectives Under Various GMR and the Number of Evaluable Participants with Immunogenicity Data Who Receives the 4th Dose in this Study (Part 2)

True GMR (mRNA-1273.214 vs. mRNA-1273 against B.1.1.529)	Number evaluable patients per arm (4th dose)	Minimum empirical GMR for the primary objective	Power
Two-sided Type I Error (α) = 0.01 (Day 29)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI [redacted]			

CCI
Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)
CCI
Two-sided Type I Error (α) = 0.04 (Month 3)
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)
CCI
Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)
CCI

Abbreviations: GMR = geometric mean titer ratio; mRNA = messenger ribonucleic acid.

4.4. Multiplicity

Statistical testing in Part 1 is independent of testing in Part 2. In each Part, the family-wise alpha of 0.05 (two-sided) will be preserved by allocating alpha across two time points: 0.01 (two-sided) at Day 29 and 0.04 (two-sided) at Month 3.

4.5. Randomization

Randomization will be performed using an interactive response technology (IRT). In Part 1, approximately 600-1000 participants will be randomized in a 1:1 ratio to receive a single dose of either 50 µg of mRNA-1273.529 or 50 µg of mRNA-1273 (active control). In Part 2, approximately 2,924 participants will be randomized in a 1:1 ratio to receive a single dose of either 50 µg of mRNA-1273.214 or 50 µg of mRNA-1273 (active control). In both parts, randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least 90% of participants will receive study vaccine as the 4th dose. There will be four randomization strata for each part:

- ≥ 16 and < 65 years, receive IP as a 4th dose
- ≥ 65 years, receive IP as a 4th dose
- ≥ 16 and < 65 years, receive IP as a 3rd dose
- ≥ 65 years, receive IP as a 3rd dose

4.6. Blinding and Unblinding

As the appearance of the study vaccines differs, enrollment will be observer-blinded as to treatment assignment.

The investigator, clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded for the final analysis. Once participants become eligible to obtain an additional booster outside of the study, they become eligible for optional unblinding and continue in Phase B of the study part they were enrolled. In Part 1, participants in either treatment arm are eligible to choose to be unblinded to study treatment after completion of the Month 6 visit. In Part 2, participants in either treatment arm are eligible to choose to be unblinded to study treatment after completion of the Month 3 visit. If a participant decides to obtain an additional booster, the booster would be obtained outside the study. Additionally, participants can choose to not be unblinded after completion of the Month 6 (Part 1) and Month 3 (Part 2) visits. All participants are encouraged to continue the study regardless of choosing to be unblinded or remain blinded and/or choosing to obtain an additional booster external to the study. The optional unblinding will be performed at the participant level by a study site member via the IRT system with all other site members remaining blinded to original treatment assignment.

At the planned analysis (see Section 6.6), pre-identified Sponsor team members and selected contract research organization (CRO) team members will be unblinded to conduct the analyses. Study participants, investigators, and blinded site personnel will remain blinded.

Planned primary analysis are described in Section 6.6 of this SAP and Section 9.7 of the protocol. Participant-level unblinding will be restricted to an independent unblinded statistician and as needed, statistical programmer(s) performing the primary analysis, who will have no other responsibilities associated with the study.

An independent unblinded statistical and programming team who are not involved in study design and conduct of the CRO will perform the planned primary analysis (Section 6.6.1). Select Sponsor team members including biostatistician and statistical programmers will be prespecified to be unblinded to the primary analysis results and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants. The details will be included in the Study Blinding Plan.

In addition to the routine study monitoring outlined in this protocol, an external DSMB will review interim safety data to safeguard the interests of clinical study participants and to enhance the integrity of the study. The DSMB will review treatment-level safety data, provided by the independent unblinded statistician. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the safety analyses, if required, to act on the recommendations of the DSMB.

The extent to which individuals are unblinded with respect to results of primary and safety analyses will be documented. The limited Sponsor and CRO team members to be unblinded in this case will be pre-specified in the study Data Blinding Plan. Participants and investigators will remain blinded until the unblinding or participant decision visit.

5. Analysis Populations

The following analysis sets are defined for each part: Randomized Set, Full Analysis Set (FAS), Modified Intent-to-Treat (mITT), PP Set for Immunogenicity (PPSI), PP Set for Immunogenicity – SARS-CoV-2 negative (PPSI-Neg), Solicited Safety Set, Safety Set, and PP Set for Efficacy (PPSE).

5.1. Randomized Set

The Randomized Set consists of all randomized participants. Participants will be analyzed according to their randomized study arm.

5.2. Full Analysis Set (FAS)

The FAS consists of all randomized participants who receive IP. Participants will be analyzed according to their randomized study arm.

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

The mITT Set consists of all participants in FAS who had no immunologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on serum binding antibody (bAb) specific to SARS-CoV-2 nucleocapsid) pre-booster, i.e., all FAS participants with pre-booster/baseline SARS-CoV-2 negative status. Participants will be analyzed according to their randomized study arm.

5.4. Per-Protocol (PP) Set for Immunogenicity (PPSI)

The PPSI consists of all participants in the FAS who received the planned dose of study vaccination and have no major protocol deviations impact critical or key study data. Participants will be analyzed according to their randomized study arm.

5.5. Per-Protocol (PP) Set for Immunogenicity – SARS-CoV-2 negative (PPSI-Neg)

The PPSI-Neg consists of participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline and up to the day of analysis visit. This is defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on the day of analysis visit AND no prior positive RT-PCR test or positive test based on bAb specific to SARS-CoV-2 nucleocapsid at baseline or between baseline and the day of analysis visit.

PPSI-Neg will be the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to their randomized study arm.

5.6. Modified Per-Protocol (PP) Set for Immunogenicity – SARS-CoV-2 negative (Modified PPSI-Neg)

The Modified PPSI-Neg consists of participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline. This is defined by both negative

RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline.

Modified PPSI-Neg will be used for sensitivity analysis of immunogenicity. Participants will be analyzed according to their randomized study arm.

5.7. Solicited Safety Set

The Solicited Safety Set consists of all randomized participants who receive IP and contribute any solicited AR (SAR) data within the first 7 Days after IP administration.

The Solicited Safety Set will be used for the analyses of SARs within 7 Days. Participants will be included in the study arm that they actually received.

5.8. Safety Set

The Safety Set consists of all randomized participants who receive IP. The Safety Set will be used for all analyses of safety except for the SARs within 7 Days. Participants will be included in the study arm that they actually received.

5.9. Per-Protocol (PP) Set for Efficacy (PPSE)

The PPSE consists of all participants in the mITT who receive the planned dose of study vaccination and have no major protocol deviations that impact key or critical data.

6. Statistical Analysis

6.1. General Considerations

Please refer to the Appendix E for Schedule of Events (SoE).

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (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 administration of IP.

For the summary statistics of all numerical variables, unless otherwise specified, the display precision will follow programming standards. Refer to Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero 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 participants corresponding group, unless otherwise specified.

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

Positive SARS-CoV-2 status prior to booster dose (baseline) is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before Day 1.

Negative SARS-CoV-2 status prior to booster dose (baseline) is defined as a no indication of a positive status based on either RT-PCR test for SARS-CoV-2 or serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at Day 1.

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

Participants with negative baseline (pre-booster) SARS-CoV-2 status will be included in the mITT population; participants with positive or missing baseline SARS-CoV-2 status will be excluded from the mITT population.

Age: unless otherwise specified, age is calculated as the age at screening.

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

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

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

The following **analysis periods** or **stages** for safety analyses will be used for both study parts:

- Up to 28 days after vaccination: from the day of vaccination (Day 1) and continues through the earliest date of (the day of vaccination and 27 subsequent days, the day of study discontinuation). This analysis period will be used as the primary analysis period for safety analyses including unsolicited AEs, except for SARs, unless specified otherwise.
- Throughout the study: from the day of vaccination (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 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 or incomplete AE dates are provided in Appendix D.
- If the laboratory results are reported as below the LLOQ, the numeric values will be substituted by 0.5 × LLOQ in the summary when treating the results as continuous variables. If the laboratory results are reported as greater than the ULOQ (e.g., > 3000), the numeric values will be substituted by ULOQ in the summary statistics for continuous variable.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups

Part 1

- mRNA-1273.529 50 µg, study vaccine as a 4th dose

- mRNA-1273 50 µg, study vaccine as a 4th dose.
- mRNA-1273.529 50 µg, study vaccine as a 3rd dose
- mRNA-1273 50 µg, study vaccine as a 3rd dose

Part 2

- mRNA-1273.214 50 µg, study vaccine as a 4th dose
- mRNA-1273 50 µg, study vaccine as a 4th dose.
- mRNA-1273.214 50 µg, study vaccine as a 3rd dose
- mRNA-1273 50 µg, study vaccine as a 3rd dose

All analyses and data summaries/displays for disposition, baseline demographics and characteristics will be provided by treatment group unless otherwise specified. All analyses and data summaries/display for efficacy will be provided by treatment group using the appropriate analysis population unless otherwise specified.

Subgroup Analysis

Immunogenicity will be assessed in the following subgroups:

- Age (≥16 to <65, and ≥65 years)
- Sex (female, male)
- SARS-CoV-2 status (negative, positive) at the day of analysis visit (e.g., for Day 29, subgroup analyses will be performed based on SARS-CoV-2 status up to Day 29 visit)
- Pre-booster SARS-CoV-2 status (negative, positive)
- Race and ethnicity group (White, Mixed or Multiple ethnic groups, Asian or Asian British, etc.)
- In addition, Phase B in each study Part (analyses may be performed in two or four subsets):
    - Two subsets
        - Subset of participants in the 4th dose group who received an additional booster outside of the study.
        - Subset of participants in the 4th dose group who did not receive an additional booster outside of the study.
    - Four subsets

- Subset of participants in the 4th dose group who were unblinded to study IP and received an additional booster outside of the study.
- Subset of participants in the 4th dose group who were unblinded to study IP and did not receive an additional booster outside of the study.
- Subset of participants in the 4th dose group who remained blinded to study IP and received an additional booster outside of the study.
- Subset of participants in the 4th dose group who remained blinded to study IP and did not receive an additional booster outside of the study.

Safety and efficacy may be assessed for the same subgroups.

Analyses Approach

All analyses and data summaries/displays will be provided by study arm (mRNA-1273.529 and mRNA-1273 for Part 1, and mRNA-1273.214 and mRNA-1273 for Part 2) and by treatment subgroups (IP administrated as 3rd or 4th dose) using the appropriate analysis population, unless otherwise specified. Data summaries for participants disposition, baseline demographics, and safety data may also be provided by treatment group.

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

Immunogenicity Measures

When referring to the immunogenicity measurement, titer, concentration, or level may be used interchangeably in this document. The appropriate measure for each measure will be specified in the study TLFs.

6.2. Background Characteristics

6.2.1. Disposition

The number and percentage of participants in the following categories (analysis sets defined in Section 5) will be summarized by treatment group as defined in Section 6.1:

- FAS
- mITT
- PPSI
- PPSI–Neg
- Solicited Safety Set
- Safety Set

- PPSE

The denominators of the percentages will be based on participants in the Full Analysis Set. The number of participants in the following categories will be summarized based on participants screened:

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

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

For Solicited Safety Set, the percentage will be based on the number of participants in the treatment group within the Safety Set (as treated).

Summary of reasons for participants excluded from PP Sets will also be provided.

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

- Received IP
- Completed study

This study treatment only consists of a one-dose booster, thus discontinuation from study treatment is not applicable in this study.

In addition, a listing of participant deaths will be provided separately.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2). The number and percentage of participants will be provided for categorical variables such as age group, sex, race, and ethnicity.

The summaries will be provided separately based on the FAS, Safety Set, and PPSI-Neg Set.

6.2.3. Medical History

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

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the 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 the sorting order described in the TLF shell document.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccinations will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set.

Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 9.

The number and percentage of participants 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 the 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 and non-study vaccination within 7 days Post Injection
- Any concomitant medications and non-study vaccination within 28 days Post Injection
- Seasonal influenza vaccine within 28 days Post Injection
- Medications to prevent pain or fever within 7 Days Post Injection
- Medications to treat pain or fever within 7 Days Post Injection

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the injection through 28 days will be provided by PT in the sorting order described in the TLF shell document.

Listings of prior, concomitant and post medications, non-study vaccination and concomitant procedures will be presented.

6.2.5. Study Exposure

Study duration, defined as time on study from the injection to study discontinuation, study completion, last contact date, or data cutoff date, whichever occurs earlier, will be summarized based on Safety Set.

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 participant's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by treatment group as defined in Section 6.1 based on the Randomized Set.

Major protocol deviations will be presented in a listing.

Selected major protocol deviations deemed to impact critical data will lead to exclusion from the PPSI or PPSE.

6.3. Safety Analysis

Following section is applicable for both Part 1 and Part 2:

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including SARs (local and systemic), unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation, vital signs, and physical examinations findings. Unsolicited AEs will be coded by SOC and PT according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study for SARs.

Safety analyses will be based on the Safety Set. The Solicited Safety Set will be used for analyses of SARs.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study that was not present before exposure to study vaccine, 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.

Refer to Protocol Appendix 3 for the definitions of AEs of special interest (AESI).

Analyses of unsolicited AEs will be summarized by stage, up to 28 days after vaccination and throughout the study and by treatment group (Section 6.1).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for TEAEs with counts of participants included. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity (the strongest causality) in the summaries by severity (of related AEs), if participants reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of participants in the Safety Set.

6.3.1.1. Incidence of Adverse Events

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

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited treatment-emergent AESIs
- Any unsolicited TEAEs that are medically-attended (MAAEs)
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any unsolicited non-serious TEAEs
- Any unsolicited severe non-serious TEAEs

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

In addition, separate listings containing individual participant data for AEs leading to death, SAEs, AESIs, and a listing of AEs prior to death in the subset of deceased participants will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

Summary tables of TEAEs by SOC and PT up to 28 days, and throughout the study after the IP administration by using frequency counts and percentages of participants with an event will be provided for:

- All unsolicited TEAEs*
- All serious TEAEs*
- All unsolicited treatment-emergent AESIs*
- All unsolicited severe TEAEs*
- All unsolicited TEAEs that are medically-attended*
- All unsolicited TEAEs leading to discontinuation from participation in the study

* Tables will also be presented for treatment-related TEAEs up to 28 days after IP administration.

6.3.2. Solicited Adverse Reactions

The SARs are recorded by the participant in eDiary on the day of injection and for the 6 days post injection. If a solicited local or systemic AR starts more than 7 days after dosing, it should be captured on the AE page until resolution, not to exceed 28 days after vaccination. If a solicited local or systemic AR continues beyond 7 days post injection, the participant should notify the site to provide an end date and close out the event. ARs beyond Day 7 should be reviewed by the clinic staff either during the next scheduled telephone call or at the next clinic visit, or during an unscheduled visit.

Analyses of SARs within 7 Days will be provided based on the Solicited Safety Set. Analyses of SARs with Onset after Day 7 will be provided based on the Safety Set. The following summaries will be provided

- Summary of SAR Within 7 Days (SAR eDiary and SAR eCRF)

  i. The number and percentage of participants who reported individual solicited local AR and/or solicited systemic AR during the 7-day follow-up period after the injection will be tabulated by severity grade, and by severity grade and day of reporting.

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

ii. The number and percentage of participants who reported individual solicited local AR and/or solicited systemic AR during the 7-day follow-up period after the injection will be summarized by onset day (Day 1 through Day 7). The onset of individual SAR is defined as the time point after the injection at which the respective SAR first occurred.

- Summary of SAR with Grade 3 or higher

  i. The number and percentage of participants who reported individual Grade 3 and/or higher solicited local AR and solicited systemic AR during the 7-day follow-up period after the injection will be tabulated by severity grade, and by severity grade and day of reporting.

- Summary of SAR Duration (SAR eDiary and SAR eCRF)

  i. The duration of SAR in days will be calculated as the last date the SAR is reported - the first date the SAR is reported + 1.

- Summary of SAR Persisting Beyond 7 Days (SAR eDiary and SAR eCRF)

  i. The number and percentage of participants who reported individual solicited local AR and/or solicited systemic AR that persist beyond 7 days after the injection (i.e., occurred before day 7, but persisting after day 7 regardless of duration) will be tabulated by severity grade.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any SAR persisting beyond 7 days after injection.

- Summary of SAR with Onset after Day 7 (AE eCRF)

  i. The incidence of solicited local ARs and solicited systemic ARs with onset day after the 7-day follow-up period after the injection (i.e., after Day 7) will be tabulated.

  ii. The onset day of solicited local ARs and solicited systemic ARs with onset day after the 7-day follow-up period after the injection (i.e., after Day 7) will be summarized descriptively.

iii. The duration of SAR in days for solicited local ARs and solicited systemic ARs with onset after the 7-day follow-up period after the injection (i.e., after Day 7) will be summarized descriptively, similar to SAR duration summary.

- Summary of Onset Day for Local Reactions (SAR eDiary and SAR eCRF)

  i. The number and percentage of participants who reported local reactions will be tabulated by onset day (within 7 days and beyond). The onset day is defined similarly in 'Summary of SAR Within 7 Days' section.

6.3.3. Pregnancy Tests

A point-of-care urine pregnancy test will be performed for all female participants of childbearing potential at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. The participant's follicle-stimulating hormone (FSH) level may be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.

A by-subject listing will be provided for pregnancy tests with positive results.

6.3.4. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be collected at the time points indicated in the SoE tables in the protocol with pre- and post-dosing on the day of injection (Day 1) only and they will be presented in a listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be provided in the listing.

If a participant 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 participant will be presented in the listing.

Shift from baseline in the toxicity grades at each time point and shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PPSI-Neg analysis population and will be performed by treatment group as defined in Section 6.1.

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

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

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

The GMFR measures the changes in immunogenicity titers within participants. The GMFR will be calculated using the following formula:

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

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

6.4.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE (Appendix E). The following immunogenicity assessments will be measured:

- Serum bAb level against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein and the S protein RBD (MSD multiplex assay).
- Serum neutralizing antibody (nAb) level against SARS-CoV-2 as measured by pseudovirus neutralization assays.

Table 5 outlines the bioassays that will be implemented to assess the immunogenicity endpoints.

With the purpose of measuring the neutralizing antibody titers against the BA.4/BA.5 variants, VAC137 assay will be analyzed as part of the exploratory analysis and will only be assessed at Day 1 and Day 29 in a randomly-selected subgroup of participants from each study part, 4th dose group only. A total of 200 participants from each study part (n=400 participants total) comprising 160 baseline SARS-CoV-2 seronegative and 40 baseline SARS-CoV-2 seropositive participants were sampled from the PPSI population. The study was stratified at randomization by age group and the distribution of participants ≥65 years was 35% in Part 1 and 33.5% and Part 2. The random sample from each study part fixed the distribution of participants ≥65 years at 35%, when feasible.

Table 5 Immunogenicity Assays

Strain/Antigen	Method	Assay Name
Prototype	Pseudovirus neutralization	VAC62
Omicron BA.1 (BA.1.1.529)	Pseudovirus neutralization	VAC122
Omicron BA.4/BA.5	Pseudovirus neutralization	VAC137
S, RBD, Omicron (B.1.1.529), Delta (AY.4), Gamma (P.1), Alpha (B.1.1.7), Beta (B.1.351)	Multiplex binding antibody ECL	MSD VAC123-8 plex

6.4.2. Analysis of the Immunogenicity Endpoints

6.4.2.1. Part 1 (mRNA-1273.529 and mRNA-1273)

6.4.2.1.1. Primary and Key Secondary Analyses

For the primary objective on immune response for the second booster (4th dose) of mRNA-1273.529, there are two primary hypotheses to be tested (see Section 4.2). The primary analysis set for immunogenicity objectives will be based on PPSI-Neg.

Day 29 (alpha=0.01, two-sided)

For the first primary hypothesis, an analysis of covariance (ANCOVA) model will be performed to assess the difference in immune response between mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 in the subgroup of participants who received the 4th dose. Antibody titers at Day 29 post-booster against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.529 and mRNA-1273) will be the fixed effect, adjusting for age groups (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA or viral vector) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the geometric least square mean (GLSM) from the model and corresponding 99% CI will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.529 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model with 99% CI. The 99% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for mRNA-1273.529 at Day 29 compared to the mRNA-1273 as a booster for non-inferiority testing.

Month 3 (alpha=0.04, two-sided)

The same ANCOVA model described above will be used to assess immune response of mRNA-1273.529 against the B.1.1.529 strain at Month 3. The 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority.

The primary immunogenicity objective (against the B.1.1.529 strain) is considered met if the non-inferiority is demonstrated based on a GMR at either Day 29 or Month 3. Specifically, against the B.1.1.529 strain, the non-inferiority of immune response of mRNA-1273.529 as compared to mRNA-1273 will be considered demonstrated if the lower bound of the corresponding 99% CI of the GMR is ≥ 0.67 (Day 29) based on a non-inferiority margin of 1.5 or the corresponding 96% CI of the GMR is ≥ 0.67 (Month 3) based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 is demonstrated, superiority of mRNA-1273.529 as compared to mRNA-1273 against B.1.1.529 will be tested (key secondary hypothesis). Specifically, superiority of mRNA-1273.529 as compared to mRNA-1273 will be demonstrated if the lower bound of the 99% CI of the GMR is >1 (Day 29) or the lower bound of the 96% CI of the GMR is >1 (Month 3).

Supportive analyses of the primary and key secondary immunogenicity endpoints at Day 29 and Month 3 will also be performed in the PPSI. These analyses will be based on the ANCOVA model described above and will include the pre-booster/baseline SARS-COV-2 status (negative, positive, or missing) as a factor. The 99% CI for GMR will be used to assess differences between groups at Day 29 and the 96% CI for GMR at Month 3.

6.4.2.1.2. Secondary Analyses

The ANCOVA model described in Section 6.4.2.1.1 will be used for secondary analyses to assess for immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 3rd or 4th dose at all measured time points. Antibody titers against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.529 and mRNA-1273) will be the fixed effect, adjusting for age groups (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA or viral vector) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the GLSM from the model and its corresponding 95% CIs will be provided for each group. The GMR for mRNA-1273.529 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 95% CIs will be provided. No hypothesis tests will be performed for these objectives.

For each antibody of interest, the GMT or level with corresponding 95% CI at each time point, and GMFR of post-baseline titers or levels over baseline with their corresponding 95% CIs at each post-baseline time point will be provided. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: number of participants (n), median, minimum, and maximum. Additionally, reverse cumulative distribution plots and box plots of titers or levels will be generated for each antibody of interest and for any subgroups of interest (e.g., age group).

The mixed effects model repeated measure (MMRM) will be used to analyze all post-booster measures including treatment group, analysis visit, treatment by visit interaction, age groups and pre-booster titer levels (if available) as fixed effects and participant as a random effect. An unstructured covariance structure will be used to model the within-participant errors. The compound symmetry structure will be used when the model fails to converge. The GMT will be estimated from the model and its corresponding 95% CI will be provided for each group at each post-boost timepoint. The GMR for mRNA-1273.529 with respect to mRNA-1273

will be estimated from the model and the corresponding 95% CI will be provided at each post-boost timepoint.

PPSI will be used as the analysis population to summarize the immune responses (antibodies of interest) and the above summary statistics including GMT and GMFR will be provided by pre-booster/study baseline SARS-CoV-2 status.

The SRR is measured by an increase of SARS-CoV-2–specific bAb or nAb titer or value (level) from pre-booster below the lower limit of quantification (< LLOQ) to at least 4 x LLOQ, or a 4-fold or greater rise if pre-booster ≥ LLOQ.

The SRR will be summarized at all measured time points for each treatment group with the 95% CI calculated using the Clopper-Pearson method. The difference of SRRs at all measured time points for mRNA-1273.529 compared with mRNA-1273 will be provided with 95% CI using Miettinen-Nurminen method. Analysis of the SRR will be performed in the PPSI-Neg. A sensitivity analysis of SRR will be performed in the PPSI by using stratified Miettinen-Nurminen method, with pre-booster positive, negative, and unknown SARS-CoV-2 status as strata.

6.4.2.1.3. Exploratory Analysis

Exploratory analyses using the same methods described above will be used to assess for immune response of mRNA-1273.529 compared to mRNA-1273 booster administered against other variant strains (e.g., Alpha, Beta, etc.) after study vaccination. Specifically, for each antibody of interest, the GMT, GMFR and SRR and corresponding 95% CI will be calculated at the time point in which immune response against other variant strains are assessed. Comparisons between booster regimens will be explored by calculating the GMR and differences in SRRs with corresponding 95% CIs, as outlined above.

Exploratory analysis will be performed of the Month 12 immune response using the same methods described above of mRNA-1273.529 compared to mRNA-1273 booster against the B.1.1.529 strain, prototype strain and other variant strains overall and by the Phase B subgroup stated in Section 6.1.

The same ANCOVA model described above may be used for exploratory analyses to assess for immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against both the B.1.1.529 and the prototype strain at Day 29, using a 95% CI for GLSM and GMR.

Similar analyses will be used to assess for immune response of mRNA-1273.529 compared to mRNA-1273 booster administered against the BA.4/BA.5 variant strains, conducted in the random sample of 200 participants. The exception will be the sensitivity analysis of SRR performed in the PPSI using the stratified Miettinen-Nurminen method, where both SARS-CoV-2 status (positive, negative, and unknown) and age group (≥16 to <65, and ≥65 years) will be included as strata.

6.4.2.2. Part 2 (mRNA-1273.214 and mRNA-1273)

6.4.2.2.1. Primary Analyses

For the primary objective on immune response for the second booster (4th dose) of mRNA-1273.214, there are six primary hypotheses to be tested (see Section 4.2). Serum neutralizing antibody will be used as the basis to assess non-inferiority and superiority in immune response. The primary analysis set for immunogenicity objectives will be based on PPSI-Neg.

Day 29 (alpha=0.01, two-sided)

The same ANCOVA model described for Part 1 will be used to assess the difference in immune response between mRNA-1273.214 and mRNA-1273 in the subgroup of participants who received the 4th dose. To test the first primary hypothesis as to if a single booster dose of mRNA-1273.214 is non-inferior to mRNA-1273 based on GMR against the B.1.1.529 strain at Day 29 an ANCOVA will be performed with antibody titers at Day 29 post-booster against the B.1.1.529 as the dependent variable, and a group variable (mRNA-1273.214 and mRNA-1273) as the fixed effect, adjusting for age groups (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA or viral vector) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the GLSM from the model and corresponding 99% CIs will be provided for each group. The GMR for mRNA-1273.214 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 99% CIs will be provided. The non-inferiority of immune response of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain for mRNA-1273.214 at Day 29 will be considered demonstrated if the lower bound of the corresponding 99% CI of the GMR is ≥ 0.67 based on a non-inferiority margin of 1.5.

The same ANCOVA model will be performed to assess the non-inferiority of immune response against the prototype strain in the subgroup of participants who received mRNA-

1273.214 and mRNA-1273 as the 4th dose (second primary hypothesis). The non-inferiority is demonstrated if the lower bound of the corresponding 99% CI of the GMR is ≥ 0.67 based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 and prototype strains is demonstrated, superiority of mRNA-1273.214 as compared to mRNA-1273 against B.1.1.529 will be tested (at Day 29). If the lower bound of the 99% CI of the GMR is > 1, superiority is demonstrated (third primary hypothesis).

Month 3 (alpha=0.04, two-sided)

The same ANCOVA model will be used to assess immune response of mRNA-1273.214 against the B.1.1.529 strain at Month 3 (fourth and six primary hypotheses). The 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority and superiority. The same ANCOVA model, and the lower bound of the corresponding 96% CI that is ≥ 0.67 based on a non-inferiority margin of 1.5 will be used to demonstrate the non-inferiority for the immune response against the prototype virus strain at Month 3 (fifth primary hypothesis).

Part 2 of this study is considered to have met its primary objective if non-inferiority of mRNA-1273.214 against the B.1.1.529 strain, non-inferiority of mRNA-1273.214 against the prototype strain, and superiority of mRNA-1273.214 against the B.1.1.529 strain are demonstrated as compared to mRNA-1273 at Day 29 or Month 3.

Supportive analyses of the primary immunogenicity endpoints at Day 29 and Month 3 will also be performed in the PPSI. These analyses will be based on the ANCOVA model described above and will include pre-booster/baseline SARS-COV-2 status (negative, positive, or missing) as a factor. The 99% CI for GMR will be used to assess differences between groups at Day 29 and the 96% CI for GMR at Month 3.

6.4.2.2.2. Secondary Analyses

The same ANCOVA model described above will be used for secondary analyses to assess for immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against other variants at Day 29 or Month 3. The GMT will be estimated by the GLSM from the model and its corresponding 95% CIs will be provided for each group. The GMR for mRNA-1273.214 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 95% CIs will be provided. No hypothesis tests will be performed for these objectives.

SRR of the mRNA-1273.214 booster administered as a 4th dose against the B.1.1.529 strain, prototype strain and other variants of concern (VOC) will be analyzed in the PPSI-Neg using the methods as described in Section 6.4.2.1.2. A sensitivity analysis of SRR will be performed in the PPSI by using stratified Miettinen-Nurminen method, with pre-booster positive, negative, and unknown SARS-CoV-2 status as strata.

MMRM as described in Section 6.4.2.1.2. will be used to assess immune response mRNA-1273.214 against both the B.1.1.529, the prototype strain, and other VOC at all measured timepoints after study vaccine administration.

6.4.2.2.3. Exploratory Analyses

Cellular immunity in a subset of participants may be assessed by evaluating the frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of T-cells and B-cells after vaccination.

The same ANCOVA model described above may be used for exploratory analyses to assess for immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against both the B.1.1.529 and the prototype strain at Day 29, using a 95% CI for GLSM and GMR.

The same ANCOVA model described above will be used for exploratory analyses to assess for immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain, the prototype strain and other variant strains at Month 6 and Month 12 overall and by Phase B subgroup stated in Section 6.1.

Additionally, the SRR will be summarized at Month 6 and Month 12 for each treatment group and by Phase B subgroup with the 95% CI calculated using the Clopper-Pearson method.

Similar analyses will be used to assess for immune response of mRNA-1273.214 compared to mRNA-1273 booster administered against the BA.4/BA.5 variant strains, conducted in the random sample of 200 participants. The exception will be the sensitivity analysis of SRR performed in the PPSI using the stratified Miettinen-Nurminen method, where both SARS-CoV-2 status (positive, negative, and unknown) and age group (≥16 to <65, and ≥65 years) will be included as strata.

6.4.2.3. Sensitivity Analyses

Sensitivity analyses may be performed on the primary immunogenicity endpoints using the Modified PPSI-Neg population and the methods described above.

If there is more than 10% missing immunogenicity data at Day 29 or Month 3, sensitivity analyses to assess the robustness of findings will be performed. The analyses will be performed in the PPSI and missing will be addressed using multiple imputation to impute missing antibody titer data assuming missing at random. The procedure is outlined as follows:

Step 1: Data imputation using Markov Chain Monte Carlo (MCMC) model including treatment group, pre-booster baseline titer, age group, Day 29/Month 3 (if applicable) antibody titer value in the log scale (with a base of 10). Should the data follow a non-monotone missing pattern, partial imputation will be performed first to create a monotone missing data pattern.

Step 2: Estimation using ANCOVA on each imputed dataset in which model includes treatment group as a fixed effect, adjusting for pre-booster baseline titer value and age group. The estimated GMR and standard errors in Log 10 scale will be estimated from each ANCOVA model.

Step 3: Pool the parameter estimates into a single estimate using Rubin's method (1987), back transform the combined estimate back to the original scale.

6.5. Efficacy Analysis

Number and incidence rates of symptomatic COVID-19 disease, asymptomatic SARS-CoV-2 infection, as well as COVID-19 regardless of symptoms will be provided for each study arm. Vaccine efficacy and the respective 95% CI will also be estimated. Efficacy analyses will be performed using the mITT and PPSE analysis populations.

Pre-booster SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1 (pre-booster).

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

In this study, the serology test results based on bAb specific to SARS-CoV-2 nucleocapsid, and the RT-PCR test results will be summarized by visit.

The primary analysis population to assess incidence of symptomatic SARS-CoV-2 infection (COVID-19), asymptomatic SARS-CoV-2 infection, and SARS-CoV-2 infection is PPSE, unless otherwise specified. mITT may be used for supportive analyses. All results will be summarized by treatment group.

Exploratory analyses for the efficacy endpoints may be performed by Phase B subgroup stated in Section 6.1.

6.5.1. Endpoint Definition/Derivation

6.5.1.1. Derivation of SARS-CoV-2 Infection

SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 status pre-booster by either:

- bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) post-baseline, OR
- Positive RT-PCR post-baseline.

The date of documented infection will be the earlier of:

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

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

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

Cases will be counted starting 14 days after the randomization, i.e., date of documented infection – date of randomization ≥ 14.
The incidence of SARS-CoV-2 infection counted starting 14 days after randomization will be summarized by treatment group.
Supportive analyses will summarize incidence of SARS-CoV-2 infection in which a case is counted after randomization, i.e., date of documented infection – date of randomization ≥ 0.

6.5.1.2. Derivation of Asymptomatic SARS-CoV-2 Infection

The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or serology tests obtained at post-baseline visits counted starting 14 days after randomization

in participants with negative SARS-CoV-2 status pre-booster. This is an exploratory endpoint in Part 1 and a secondary endpoint in Part 2.

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

- Absence of COVID-19 symptoms +/- 14 days from the positive test below
- AND at least one from below:
  - bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, or
  - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits)

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

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

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

6.5.1.3. Derivation of Symptomatic SARS-CoV-2 Infection (COVID-19)

The incidence of symptomatic SARS-CoV-2 infection starting 14 days after randomization is an exploratory endpoint in Part 1 and a secondary endpoint in Part 2. Surveillance for COVID-19 symptoms will be conducted via safety calls throughout the duration of the study and blood draw from scheduled visits. Participants reporting certain COVID-19 symptoms will be arranged an unscheduled visit to collect an NP swab.
Symptomatic SARS-CoV-2 infection will be defined in the following two ways:

1. Protocol-defined COVID-19 case definition (primary case definition): Cases to be defined as meeting clinical criteria based on both symptoms of COVID-19 and positive RT-PCR test results as outlined in Table 6.
2. CDC Case Definition of COVID-19 (secondary case definition): Cases 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 7.

Table 6 Derivation of Symptomatic COVID-19 (primary case definition)

Post-baseline PCR results	Positive, **AND**
Systemic Symptoms	at least TWO of the following **systemic symptoms**: Fever (≥ 38ºC/≥ 100.4º F), chills, muscle and/or body aches (not related to exercise), headache, sore throat, new loss of taste/smell; **OR**
Respiratory Symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath and/or difficulty breathing, OR clinical or radiographical evidence of pneumonia.

Table 7 Derivation of Symptomatic COVID-19 (secondary case definition)

	COVID-19 (CDC criteria)
Post-baseline PCR results	Positive, **AND**
Systemic Symptoms	at least **ONE** of the following systemic symptoms: Fever (temperature ≥ 38º C/≥ 100.4º F) or chills, fatigue, muscle and/or body aches (unrelated to exercise), headache, congestion or runny nose, new loss of taste or smell, sore throat, or vomiting or diarrhea; **OR**
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath or difficulty breathing.

The date of documented COVID-19 (case) will be the later date of the eligible symptom(s) and date of positive PCR test and the two dates should be within 14 of each other. Specifically, for the primary definition, the date of the documented COVID-19 will be later date of:

- Date of the positive RT-PCR test,
- Date of eligible symptom(s), defined as earliest of
    - Systemic symptoms: earliest date of the 2nd eligible systemic symptom is reported
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported

For the secondary definition of a COVID-19 infection, the date of documented COVID-19 will be the later date of:

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

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

Date of documented Case Definition of COVID-19 – Date of randomization + 1.

Cases will be counted starting 14 days post randomization, i.e., date of documented COVID-19 – Date of randomization ≥ 14.

6.5.2. Analysis Method

The number and percentage of participants who had each type of event (i.e., an asymptomatic or a symptomatic SARS-CoV-2 infection) will be summarized in the PPSE.

As per Phase B, participants are allowed to receive an additional booster outside of the study. Participants who received this additional booster may be censored in the efficacy analyses at the time of booster, as outlined below.

The incidence rate of each type of event will be calculated as the number of cases divided by the total person-time. Person-time is defined as the total time from randomization date to the date of event, last date of study participation, censoring time, date of additional booster outside of the study or efficacy data cutoff date, whichever is earlier.

The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Vaccine efficacy and the respective 95% CI will also be estimated.

6.5.3. Sensitivity Analysis of Efficacy Endpoints

Sensitivity analysis for the efficacy endpoints may be performed with the same methods described above based on the mITT Set and with cases counted starting at different time points.

A sensitivity analysis will be performed based on a modified version of the primary and secondary definition substituting positive lateral flow test for PCR test.

A sensitivity analysis will be performed based on a modified version of the primary and secondary definition including positive lateral flow test and positive PCR test.

6.5.4. SARS-CoV-2 Symptoms and COVID-19 Severity

SARS-CoV-2 reported symptoms assessment will be assessed during the study and provided in a listing.
COVID-19 severity will also be assessed, and a listing will be provided.

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

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

6.6. Planned Analyses

The planned interim analyses of immunogenicity and safety will be performed after participants have completed Day 29 and Month 3 in both Part 1 and Part 2. Analyses of the Month 6 and Month 12 visit including Phase B (open-label, observational) will be exploratory. The final analysis of all endpoints will be performed after all participants have completed or discontinued from the study. Results of the final analysis will be presented in a final clinical study report (CSR).

6.7. Data Safety Monitoring Board (DSMB)

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and contract research organization (CRO) medical monitor, as well as safety reviews by an unblinded Data and Safety Monitoring

Board (DSMB). The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB, composed of external, independent subject matter experts, including an unblinded statistician (non-voting), will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

An independent Cardiac Event Adjudication Committee (CEAC) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events and provide the assessment to the Sponsor. The CEAC members will be blinded to study vaccine assignment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

7. Changes from Planned Analyses in Protocol

Not applicable.

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 2021 Oct 18] [10 screens]. Available from: https://www.fda.gov/media/73679/download.

Rubin, D. B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons.

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 one decimal place. If the count is zero, 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 participants 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
Humoral Immunogenicity		
Baseline (Day 1)	1 (Date of Injection)	≤1
Day 29 (Month 1)	29	[2, 57]
Day 85 (Month 3)	85	[58, 132]
Day 179 (Month 6)	179	[133, 269]
Day 359 (Month 12)	359	≥270
Cellular Immunogenicity (subset of participants in Part 2 only)		
Baseline (Day 1)	1 (Date of Injection)	≤1
Day 8	8	≥2

9.3. Appendix C Imputation Rules for Missing Dates of Prior/Concomitant Medications, Non-Study Vaccinations and Prior COVID-19 Vaccination

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

In summary, the prior, concomitant or post categorization of medications and non-study vaccinations is described in the table below.

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

	Medication Stop Date		
Medication Start Date	**< Injection Date of IP**	**≥ Injection Date and ≤ 27 Days After Injection**	**> 27 Days After Injection [2]**
< Injection date of IP [1]	P	P, C	P, C, A
≥ Injection date and ≤ 27 days after injection	-	C	C, A
> 27 days after injection	-	-	A

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

3. Missing or partial dates for prior COVID-19 vaccines:

    a. If only Day is missing, impute the first day of the month.

    b. No imputation for missing month, year or month and year.

    c. If Day, Month, and Year are all missing, the date will not be imputed.

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 injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date and time of 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 injection or is missing/partial AND the start year of the AE coincides with the start year of the injection. In this case, use the date and time of 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 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

Table 10 Schedule of Events Part 1

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
ICF, demographics, concomitant medications, medical history[2]	X										
Confirm participant meets inclusion and exclusion criteria	X	X									
Physical examination[3]	X	X				X	X	X		X	X
Vital signs[4]	X	X									X
Pregnancy testing[5]	X	X									
Randomization		X									

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Dosing											
Study injection (including 15-minute post-dosing observation period)		X									
Surveillance for COVID-19											
Surveillance for COVID-19/Unscheduled visit[6]	X	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal swab[6]		X				X	X	X		X	X
Blood for SARS-CoV-2 surveillance		X				X	X	X		X	
eDiary activation for surveillance for COVID-19/Unscheduled visit						X					

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
eDiary prompts every 2 weeks for surveillance for COVID-19 and major changes in health						eDiary prompts every 2 weeks (Day 43 through Day 359/EoS)					
Immunogenicity Assessment											
Blood for humoral immunogenicity[7]		X				X	X	X		X	

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Safety Assessments											
eDiary activation for recording solicited adverse reactions (7 days)[8]		X									
Review of eDiary			X								
Follow-up safety			X	X	X				X		
Recording of Unsolicited AEs		X	X	X	X	X					
Recording of MAAEs, AESIs, AE leading to withdrawal and concomitant medications relevant to or for the treatment of these events[9]		X	X	X	X	X	X	X	X	X	X

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[9]		X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations[10]		X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; EoS = end of study; ICF = informed consent form; M = month; MAAE = medically attended AE; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (phone) call; USV = unscheduled safety visit.

All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on-site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications. Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site.

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.

3. Physical examination: a full physical examination, including vital signs, height, and weight, will be performed at Screening and Day 1. Body mass index will be calculated at the Screening Visit only. Symptom-directed physical examinations will be performed on Day 29, Day 85, Day 179, D359/EoS, and during USV visits. On the day of the vaccination, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as a MAAE.
4. Vital signs measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 15 minutes after vaccination. When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before dosing must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination. A pulse oximeter measurement may be performed at the unscheduled visit, if applicable/available.
5. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating hormone level should be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.
6. An unscheduled visit may be prompted by reactogenicity issues, illness visit for COVID-19, or new or ongoing AEs. If a participant experiences symptoms suggestive of COVID-19, the participant will be directed as soon as possible and within 24 hours to undergo testing as outlined in Section 8.9.2 of the protocol. An unscheduled study illness visit will be arranged as soon as possible and within 72 hours for participants who test positive for SARS-CoV-2 as per testing as outlined in Section 8.9.2 of the protocol. At this visit, an NP swab will be collected to evaluate for the presence of SARS-CoV-2 infection. If a study site visit is not possible, a home visit may be arranged to collect a swab sample and conduct clinical evaluations. Additionally, clinical information will be collected to evaluate the severity of the clinical case.
7. Samples for humoral immunogenicity must be collected prior to receipt of vaccination on Day 1. All participants will have blood drawn for humoral immunogenicity.
8. The participant will record data in the eDiary approximately 15 minutes after dosing while at the study site, with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of dosing, and for 6 days following. Any solicited AR that is ongoing beyond Day 7 will be reported verbally by participants at the scheduled Safety Calls, until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. Participants will be given thermometers to record their body temperatures and rulers to measure any injection site reactions.
9. Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations.
10. All concomitant medications and non-study vaccinations will be recorded through 28 days after vaccination, except authorized or investigational COVID-19 vaccine(s) given at any time during the study period should be recorded (Day 29 through EoS).

Table 11 Schedule of Events Part 2

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
ICF, demographics, concomitant medications, medical history[2]	X										
Confirm participant meets inclusion and exclusion criteria	X	X									
Physical examination[3]	X	X	X			X	X	X		X	X
Vital signs[4]	X	X									X
Pregnancy testing[5]	X	X									
Randomization		X									
Dosing											

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Study injection (including 15-minute post-dosing observation period)		X									

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Surveillance for COVID-19											
Surveillance for COVID-19/Unscheduled visit[6]	X	X	X	X	X	X	X	X	X	X	X
Nasopharyngeal swab[6]		X				X	X	X		X	X
Blood for SARS-CoV-2 surveillance		X				X	X	X		X	
eDiary activation for surveillance for COVID-19/Unscheduled visit						X					
eDiary prompts every 2 weeks for surveillance for COVID-19 and major changes in health						eDiary prompts every 2 weeks (Day 43 through Day 359/EoS)					

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Immunogenicity Assessment											
Blood for humoral immunogenicity[7]		X				X	X	X		X	
Blood for cellular immunogenicity in a subset of participants[7]		X	X								
Safety Assessments											
eDiary activation for recording solicited adverse reactions (7 days)[8]		X									
Review of eDiary			X								
Follow-up safety			X	X	X				X		
Recording of Unsolicited AEs		X	X	X	X	X					

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
Recording of MAAEs, AESIs, AE leading to withdrawal and concomitant medications relevant to or for the treatment of these events[9]		X	X	X	X	X	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[9]		X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations[10]		X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; EoS = end of study; ICF = informed consent form; M = month; MAAE = medically attended AE; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (phone) call; USV = unscheduled safety visit.

All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on-site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications. Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site.

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.
3. Physical examination: a full physical examination, including vital signs, height, and weight, will be performed at Screening and Day 1. Body mass index will be calculated at the Screening Visit only. Symptom-directed physical examinations will be performed on Day 8 (if applicable), Day 29, Day 85, Day 179, D359/EoS, and during USV visits. On the day of the vaccination, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as a MAAE.
4. Vital signs measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 15 minutes after vaccination. When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before dosing must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination. A pulse oximeter measurement may be performed at the unscheduled visit, if applicable/available.
5. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating hormone level should be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.
6. An unscheduled visit may be prompted by reactogenicity issues, illness visit for COVID-19, or new or ongoing AEs. If a participant experiences symptoms suggestive of COVID-19, the participant will be directed as soon as possible and within 24 hours to undergo testing as outlined in Section 8.9.2 from the protocol. An unscheduled study illness visit will be arranged as soon as possible and within 72 hours for participants who test positive for SARS-CoV-2 as per testing as outlined in Section 8.9.2 from the protocol. At this visit, an NP swab will be collected to evaluate for the presence of SARS-CoV-2 infection. If a study site visit is not possible, a home visit may be arranged to collect a swab sample and conduct clinical evaluations. Additionally, clinical information will be collected to evaluate the severity of the clinical case.
7. Samples for humoral immunogenicity and cellular immunogenicity (if applicable) must be collected prior to receipt of vaccination on Day 1. All participants will have blood drawn for humoral immunogenicity. Only a subset of participants who will receive the 4th dose as the study vaccine will have blood drawn for cellular immunogenicity.
8. The participant will record data in the eDiary approximately 15 minutes after dosing while at the study site, with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of dosing, and for 6 days following. Any solicited AR that is ongoing beyond Day 7 will be reported verbally by participants at the scheduled Safety Calls, until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. Participants will be given thermometers to record their body temperatures and rulers to measure any injection site reactions.
9. Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations.

10. All concomitant medications and non-study vaccinations will be recorded through 28 days after vaccination, except authorized or investigational COVID-19 vaccine(s) given at any time during the study period should be recorded (Day 29 through EoS).

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTx, Inc.**
Protocol Number:	**mRNA-1273-P305**

Document Description:	Statistical Analysis Plan
SAP Title:	A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine
SAP Version Number:	5.0
Effective Date:	12SEPT2023

Author(s):

For PPD: PPD

PPD

PPD

Date *(DD-MMM-YYYY)*

PPD

Date *(DD-MMM-YYYY)*

PPD

Date *(DD-MMM-YYYY)*

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Certificate Of Completion

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Status: Original
27-Sep-2023 | 13:39
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Sep-2023 | 13:40 Viewed: 27-Sep-2023 | 14:34 Signed: 27-Sep-2023 | 14:35
Electronic Record and Signature Disclosure: Accepted: 09-Aug-2022 | 09:05 ID: PPD		
PPD Security Level: Email, Account Authentication (Required), Login with SSO	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Sep-2023 | 13:40 Viewed: 27-Sep-2023 | 13:42 Signed: 27-Sep-2023 | 13:43
Electronic Record and Signature Disclosure: Accepted: 15-Feb-2022 | 16:35 ID: PPD		

Signer Events	Signature	Timestamp
PPD ModernaTX, Inc. - Regulated Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Sep-2023 | 13:40 Viewed: 27-Sep-2023 | 13:51 Signed: 27-Sep-2023 | 13:52
Electronic Record and Signature Disclosure: Accepted: 19-Jul-2022 | 20:46 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	27-Sep-2023 | 13:40
Certified Delivered	Security Checked	27-Sep-2023 | 13:51
Signing Complete	Security Checked	27-Sep-2023 | 13:52
Completed	Security Checked	27-Sep-2023 | 14:35

Payment Events	Status	Timestamps

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