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ModernaTX, Inc.

Protocol mRNA-1273-P205

A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants

Statistical Analysis Plan

SAP Version 7.0
Version Date of SAP: 09 Jan 2024

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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
BMI	body mass index
bAb	binding antibody
CI	confidence interval
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
eCRF	electronic case report form
eDiary	electronic diary
EUA	Emergency Use Authorization
FAS	full analysis set
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMR	geometric mean ratio
IP	investigational product
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model repeated measure
MN	Miettinen-Nurminen
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PP	per-protocol
PI	principal investigator
PPIS	per-protocol immunogenicity set
PPIS-Neg	per-protocol immunogenicity SARS-CoV-2 negative set
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	system organ class
SoE	schedule of events
SRR	seroresponse rate
TEAE	treatment-emergent adverse event

Abbreviation	Definition
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 7.0, is based on the clinical study protocol (CSP), Amendment 11, dated 10-Oct-2023 and the most recently approved electronic case report form (eCRF) Release 27, dated 11-Oct-2023. The main purpose of this SAP amendment is to align with CSP Amendment 11: 1) remove immunogenicity objectives and endpoints that are no longer applicable due to the updated FDA guidance on emergency use authorization for vaccines to prevent COVID-19 (FDA 2022) and 2) remove antibody response comparisons between different vaccines as each modified vaccine targets a specific variant of concern that is no longer in circulation. Hence, comparing antibody responses between such vaccines is deemed not clinically meaningful.

Table 1: Summary of major changes in SAP Version 7.0

Section	Brief Description of Changes	Rationale
2.1 (Primary Objectives), 2.2 (Secondary Objectives), 2.3 (Exploratory Objectives)	Updated primary, secondary, and exploratory objectives.	Updated according to protocol amendment 11.
3.1 (Primary Endpoints), 3.2 (Secondary Endpoints), 3.3 (Exploratory Endpoints)	Updated primary, secondary, and exploratory endpoints.	Updated according to protocol amendment 11.
4.1 (Overall Study Design), 4.2 (Statistical Hypotheses), 4.3 (Sample Size and Power)	Updated details for multiple parts.	Updated according to protocol amendment 11.
4.6 (Sampling Plan for Selecting 301 (COVE) Subjects)	Section removed and subsequent sections renumbered.	Updated according to protocol amendment 11.
5 (Analysis Sets)	Added All Enrolled Set, removed mITT Set, and updated existing analysis set names.	Updated according to protocol amendment 11 and final analysis scope.
6.4.1 (Immunogenicity Assessments)	New table added to specify immunogenicity tests performed.	Updated to clarify the variants and time points tested for each part.

6.4.2 (Selecting P201B Subjects as External Comparator)	Removed P301 (COVE) study as historical control for Study Parts A.1, B, C, and D.	No longer applicable per protocol amendment 11.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints), 6.4.4 (Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints), 6.4.5 (Exploratory Analysis of Antibody-Mediated Immunogenicity Endpoints)	Removed analyses that are no longer applicable.	Updated according to protocol amendment 11.
6.5.5 (Sequencing)	New section added.	Added analysis strategy for exploratory objective.

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. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

Study mRNA-1273-P205 is a phase 2/3, open-label study to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1273.211, mRNA-1273, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815, and mRNA-1273.231 vaccines. The study consists of 9 parts: Part A.1 will evaluate 2 dose levels (50 or 100 µg) of mRNA-1273.211, Part B will evaluate a single dose of 100 µg mRNA-1273, Part C will evaluate 2 dose levels (50 or 100 µg) of mRNA-1273.617.2, Part D will evaluate 2 dose levels (50 or 100 µg) of mRNA-1273.213, Part E will evaluate a single dose of 100 µg mRNA-1273.213 at a single clinical study site, Part F Cohort 1 will evaluate 50 µg of mRNA-1273.529 as a single booster, Part F Cohort 2 will evaluate 50 µg of the mRNA-1273.529 vaccine or 50 µg of the mRNA-1273 as a second booster in individuals who have previously received a single booster dose of 50 µg mRNA-1273, Part G will evaluate 50 µg of mRNA-1273.214 as a second booster in individuals who have previously received a single booster dose of 50 µg mRNA-1273, Part A.2 will evaluate 50 µg of mRNA-1273.214 as a second booster in individuals who have previously received the mRNA-1273.211 booster, Part H will evaluate 50 µg of mRNA-1273.222 as a second

booster in individuals who have previously received a single booster dose of 50 µg mRNA-1273, and Part J will evaluate 50 µg of mRNA-1273.815 or 50 µg of mRNA-1273.231 as a booster in individuals who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2.

The PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the immunogenicity, safety, reactogenicity and efficacy data. SAS version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets).

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

2. Study Objectives

2.1. Primary Objectives

This study consists of 9 parts: A (1, 2), B, C, D, E, F, G, H and J. The primary objectives for each study part are the following:

Part A.1

50 µg mRNA-1273.211 and 100 µg mRNA-1273.211:

- To evaluate the safety and reactogenicity of mRNA-1273.211.

Part A.2

Second booster dose 50 µg mRNA-1273.214 for participants who received mRNA-1273.211 50 µg as a first booster dose in Part A.1:

- To evaluate the immunogenicity of mRNA-1273.214 (50 µg) as a second booster dose in participants who previously received a first booster dose of mRNA-1273.211 (50 µg).
- To assess the safety and reactogenicity of the mRNA-1273.214 (50 µg) given as a second booster dose in participants who previously received a first booster dose of mRNA-1273.211 (50 µg).

Part B

100 µg mRNA-1273:

- To evaluate the safety and reactogenicity of mRNA-1273.

Part C

50 µg mRNA-1273.617.2 and 100 µg mRNA-1273.617.2:

- To evaluate the safety and reactogenicity of mRNA-1273.617.2.

Part D

50 µg of mRNA-1273.213 and 100 µg mRNA-1273.213:

- To evaluate the safety and reactogenicity of mRNA-1273.213.

Part E

100 µg mRNA-1273.213:

- To evaluate the safety and reactogenicity of mRNA-1273.213.

Part F (Cohort 1)

50 µg mRNA-1273.529 for participants who previously received 100 µg primary series and have not received a mRNA-1273 booster dose previously:

- To demonstrate non-inferiority of the antibody response against the Omicron variant (B.1.1.529) of a first booster dose of mRNA-1273.529 compared to a first booster dose of mRNA-1273 (50 µg) based on GMT ratio and SRR difference.
- To demonstrate superiority of the antibody response against the Omicron variant (B.1.1.529) of a first booster dose of mRNA-1273.529 compared to a first booster dose of mRNA-1273 (50 µg) based on GMT ratio.
- To evaluate the safety and reactogenicity of mRNA-1273.529.

Part F (Cohort 2)

Second booster dose of 50 µg mRNA-1273.529 or 50 µg mRNA-1273 for participants who previously received 100 µg primary series and a booster dose of 50 µg mRNA-1273:

- To demonstrate non-inferiority of the antibody response against the Omicron variant (B.1.1.529) of a second booster dose of mRNA-1273.529 compared to a second booster dose of mRNA-1273 (50 µg) based on GMT ratio and SRR difference.
- To demonstrate superiority of the antibody response against the Omicron variant (B.1.1.529) of a second booster dose of mRNA-1273.529 compared to a second booster dose of mRNA-1273 (50 µg) based on GMT ratio.
- To evaluate the safety and reactogenicity of mRNA-1273.529.

Part G

Second booster dose of 50 µg mRNA-1273.214 for participants who previously received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273:

- To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) when administered as a second booster dose against the Omicron variant (B.1.1.529) based on GMT ratio and SRR difference at Day 29 and Day 91.
- To demonstrate superiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) when administered as a second booster dose against the Omicron variant (B.1.1.529) based on GMT ratio at Day 29 and Day 91.
- To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) when administered as a second booster dose against the ancestral SARS-CoV-2 based on GMT ratio at Day 29 and Day 91.
- To evaluate the safety and reactogenicity of mRNA-1273.214.

Part H

Second booster dose of 50 µg mRNA-1273.222 for participants who previously received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273:

- To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a

second booster dose against the Omicron BA.4/5 based on GMT ratio and SRR difference at Day 29.

- To demonstrate superiority of the antibody response of a second booster dose of mRNA-1273.222 compared to mRNA-1273 (50 µg) administered as a second booster dose against the Omicron BA.4/5 based on GMT ratio at Day 29.
- To demonstrate non-inferiority of the antibody response of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second booster dose against the ancestral SARS-CoV-2 D614G based on GMT ratio and SRR difference at Day 29.
- To evaluate the safety and reactogenicity of mRNA-1273.222 50 µg.

Part J

Booster dose of mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg) for participants who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2:

- To evaluate the immunogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg) against SARS-CoV-2 Omicron BA.4/BA.5, BQ.1.1, and XBB.1.5 subvariants at Day 15 and Day 29.
- To evaluate the safety and reactogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg).

2.2. Secondary Objectives

The secondary objectives will be assessed for each dose level in each study part and are described below:

Part A.2

- To evaluate the immunogenicity of mRNA-1273.214 (50 µg) as a second booster dose in participants who previously received a first booster dose of mRNA-1273.211 (50 µg).

Part E

- To evaluate the immune response of 100 µg mRNA-1273.213 as booster against the ancestral SARS-CoV-2 and variants at a single clinical study site.

Part F (Cohort 1)

- To evaluate the immunogenicity of a mRNA-1273.529 dose compared to a mRNA-1273 administered as a first booster dose at selected timepoints post-boost.

Part F (Cohort 2)

- To evaluate the immunogenicity of a mRNA-1273.529 booster compared to mRNA-1273 booster administered as a second booster dose at selected timepoints post-boost.

Part G

Key secondary objective:

- To demonstrate non-inferiority based on the SRR against ancestral SARS-CoV-2 of a second booster dose of mRNA-1273.214 compared to a second booster dose of mRNA-1273 (50 µg) at Day 29 and Day 91.

Secondary objective:

- To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a second booster dose at selected timepoints post-boost.

Part H

- To evaluate the immunogenicity of mRNA-1273.222 50 µg as a second booster dose against the ancestral SARS-CoV-2 (and other variants) compared to a second booster dose of mRNA-1273 50 µg at selected timepoints post-boost.

2.3. Exploratory Objectives

The common exploratory objectives shared by all study parts (A.1, A.2, B, C, D, E, F, G, H and J) is the following:

- To assess for symptomatic and asymptomatic SARS-CoV-2 infection.

The common exploratory objectives shared by study parts A.1, A.2, B, C, D, E, F, G, and H is the following:

- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.

The exploratory objectives that are specific to each study part are as follows:

Part A.1

- To evaluate the immunogenicity of mRNA-1273.211 at selected timepoints post-boost.

Part B

- To evaluate the immunogenicity of mRNA-1273 at selected timepoints post-boost.

Part C

- To evaluate the immunogenicity of mRNA-1273.617.2 at selected timepoints post-boost.

Part D

- To evaluate the immunogenicity of mRNA-1273.213 at selected timepoints post-boost.

Part F (Cohort 1 and 2)

- To characterize the cellular immune response of mRNA-1273.529 as a booster against the ancestral SARS-CoV-2 and other variants.

Part G

- To characterize the cellular immune response of mRNA-1273.214 as a booster against the ancestral SARS-CoV-2 and other variants.

Part J

- To evaluate the immunogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg) against SARS-CoV-2 variants at selected timepoints.

3. Study Endpoints

3.1. Primary Endpoints

The primary immunogenicity objectives will be evaluated by the following endpoints for each study part:

Part A.2

- GMT ratio and SRR difference of mRNA-1273.214 (50 µg) as a second booster dose against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants

(including Omicron) compared to mRNA-1273.211 (50 µg) against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants as the first booster dose at Day 29 and Day 181

Part F (Cohort 1)

50 µg mRNA-1273.529 for participants who previously received 100 µg primary series and have not received a mRNA-1273 booster dose previously:

- Day 29 post-boost GMT ratio of Omicron-specific GMT of mRNA-1273.529 over the Omicron-specific GMT of mRNA-1273 (historical mRNA-1273 booster dose control)
- Day 29 SRR difference between mRNA-1273.529 against Omicron and mRNA-1273 against Omicron

Part F (Cohort 2)

Second booster dose of 50 µg mRNA-1273.529 or 50 µg mRNA-1273 for participants who previously received 100 µg primary series and one booster dose of 50 µg mRNA-1273:

- Day 29 post-boost GMT ratio of Omicron-specific GMT of mRNA-1273.529 over the Omicron-specific GMT of mRNA-1273
- Day 29 SRR difference between mRNA-1273.529 against Omicron and mRNA-1273 against Omicron

Part G

Second booster dose of 50 µg mRNA-1273.214 for participants who previously received 100 µg primary series and one booster dose of 50 µg mRNA-1273:

- GMT ratio of Omicron-specific GMT of mRNA-1273.214 over the Omicron-specific GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91
- SRR difference between mRNA-1273.214 against Omicron variant and mRNA-1273 against Omicron variant at Day 29 and Day 91

- GMT ratio of ancestral SARS-CoV-2 GMT of mRNA-1273.214 over the ancestral SARS-CoV-2 GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91

Part H

Second booster dose of 50 µg mRNA-1273.222 for participants who previously received 100 µg primary series and a booster dose of 50 µg mRNA-1273:

- GMT ratio of Omicron BA.4/5 GMT of mRNA-1273.222 over the Omicron BA.4/5 GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29
- SRR difference between mRNA-1273.222 against Omicron BA.4/5 and mRNA-1273 against Omicron BA.4/5 at Day 29
- GMT ratio of the ancestral SARS-CoV-2 D614G GMT of mRNA-1273.222 over the ancestral SARS-CoV-2 D614G GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29
- SRR difference between mRNA-1273.222 and mRNA-1273 against the ancestral SARS-CoV-2 D614G at Day 29

Part J

Booster dose of mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg) for participants who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2:

- Antibody response of mRNA-1273.815 (50 µg) and mRNA-1273.231(50 µg) against SARS-CoV-2 Omicron BA.4/BA.5, BQ.1.1, and XBB.1.5 subvariants by GMT, geometric mean fold rise (GMFR), and SRR at Day 15 and Day 29

The primary safety objective will be evaluated by the following endpoints for all study parts (A.1, A.2, B, C, D, E, F, G, H and J):

- Solicited local and systemic reactogenicity adverse reactions (ARs) during a 7-day follow-up period after vaccination

- Unsolicited adverse events (AEs) during 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

The secondary objectives for each dose level in each study part will be evaluated by the following endpoints:

Part A.2

- Antibody response of the mRNA-1273.214 (50 µg) against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants (including Omicron) by GMT and SRR at multiple time points after the mRNA-1273.214 booster dose

Part E

- Immune response of 100 µg mRNA-1273.213 against the ancestral SARS-CoV-2 and variants at all timepoints by GMT, geometric mean fold rise (GMFR), and SRR

Part F (Cohort 1 and 2)

- GMT ratio of mRNA-1273.529 and mRNA-1273 against the Omicron variant at selected timepoints post-boost
- SRR difference between mRNA-1273.529 against the Omicron variant and mRNA-1273 against the Omicron variant
- GMT ratio of mRNA-1273.529 and mRNA-1273 against the ancestral SARS-CoV-2 and other variants at selected timepoints post-boost
- SRR difference between mRNA-1273.529 against the ancestral SARS-CoV-2 and other variants and mRNA-1273 against the ancestral SARS-CoV-2 and other variants

Part G

Key secondary endpoint:

- SRR difference between mRNA-1273.214 against ancestral SARS-CoV-2 and mRNA-1273 against ancestral SARS-CoV-2 at Day 29 and Day 91

Secondary endpoints:

- GMT ratio of mRNA-1273.214 and mRNA-1273 against the Omicron variant at selected timepoints post-boost
- SRR difference between mRNA-1273.214 against the Omicron variant and mRNA-1273 against the Omicron variant at selected timepoints post-boost
- GMT ratio of mRNA-1273.214 and mRNA-1273 against the ancestral SARS-CoV-2 and other variants at selected timepoints post-boost
- SRR difference between mRNA-1273.214 against the ancestral SARS-CoV-2 and other variants and mRNA-1273 against the ancestral SARS-CoV-2 and other variants at selected timepoints post-boost

Part H

- GMT ratio of mRNA-1273.222 50 µg and mRNA-1273 50 µg against ancestral SARS-CoV-2 (and other variants) at selected timepoints post-boost
- SRR difference between mRNA-1273.222 50 µg and mRNA-1273 50 µg against ancestral SARS-CoV-2 and variants of concern at selected timepoints post-boost

3.3. Exploratory Endpoints

The common exploratory endpoints shared by all study parts (A.1, A.2, B, C, D, E, F, G, H and J) are the following:

- Laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants:
    - Primary case definition per the P301 (COVE) study
    - Secondary case definition based on the 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 reverse transcriptase polymerase chain reaction (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 anti-nucleocapsid antibody after a negative test at time of enrollment

The common exploratory endpoints shared by study parts A.1, A.2, B, C, D, E, F, G and H) are the following:

- Characterization of the SARS-CoV-2 spike genetic sequence of viral isolates and comparison with the vaccine sequence

Exploratory endpoints for each dose level unique to each study part are the following:

Part A.1

- Immune response of mRNA-1273.211 against ancestral SARS-CoV-2 and SARS-CoV-2 variants including B.1.351 at selected timepoints post-boost by GMT, GMFR and SRR

Part B

- Immune response of mRNA-1273 against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants at selected timepoints post-boost by GMT, GMFR, and SRR

Part C

- Immune response of mRNA-1273.617.2 against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants including B.1.617.2 at selected timepoints post-boost by GMT, GMFR, and SRR

Part D

- Immune response of mRNA-1273.213 against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants including B.1.351 and B.1.617.2 at selected timepoints post-boost

Part F (Cohort 1 and 2)

- T-cell and B-cell response after the mRNA-1273.529 booster

Part G

- T-cell and B-cell response after the mRNA-1273.214 booster

Part J

- Antibody response of mRNA-1273.815 (50 μg) and mRNA-1273.231(50 μg) against SARS-CoV-2 variants by GMT, GMFR, and SRR at selected timepoints

4. Study Design

4.1. Overall Study Design

This is an open-label, Phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1273.211 (Part A.1), mRNA-1273 (Part B and F), mRNA-1273.617.2 (Part C), mRNA-1273.213 (Part D and E), mRNA-1273.529 (Part F), mRNA-123.214 (Part G and Part A.2), mRNA-1273.222 (Part H), mRNA-1273.815 (Part J) and mRNA-1273.231 (Part J) vaccines.

Part A.1

Part A.1 will evaluate two dose levels (50 or 100 µg total mRNA content) of the mRNA-1273.211 vaccine administered as a single booster dose to adult participants of the mRNA-1273-P301 (COVE) study who have previously received 2 doses of mRNA-1273 as a primary series. Enrollment will begin with the 50 µg dose arm, followed by the 100 µg dose arm.

Part A.2

Part A.2 will evaluate the immunogenicity, safety, and reactogenicity of the mRNA-1273.214 vaccine administered as a second booster dose to adult participants of the mRNA-1273-P205 study who have previously received 2 doses of mRNA-1273 as a primary series and a first booster of (50 µg total mRNA content) of the mRNA-1273.211 in Part A.1 of this study.

Part B

Part B will evaluate a single dose of mRNA-1273 100 µg vaccine administered as a single booster dose to adult participants of the mRNA-1273-P301 (COVE) study who have previously received 2 doses of mRNA-1273 as a primary series. Enrollment will begin upon the completion of enrollment of Part A.1 of the study.

Part C

Part C will evaluate two dose levels (50 or 100 µg) of the mRNA-1273.617.2 vaccine administered as a single booster dose to adults who have previously received 2 doses of mRNA-1273 as a primary series in Study mRNA-1273-P301 (COVE) or under the EUA. Enrollment of the 100 µg dose arm will begin upon completion of enrollment of Part B of

the study and the 50 µg dose arm enrollment will begin after completion of the 100 µg dose level arm in both Part C and D.

Part D

Part D will evaluate two dose levels (50 or 100 µg) of the mRNA-1273.213 vaccine administered as a single booster dose to adults who have previously received 2 doses of mRNA-1273 as a primary series in Study mRNA-1273-P301 (COVE) or under the EUA. Enrollment of the 100 µg dose level arm will begin upon completion of enrollment of Part C 100 µg dose level arm of the study followed by the 50 µg dose arm, which may run in parallel with Part C 50 µg dose arm enrollment.

Part E

Part E will be enrolled at a single clinical study site and will evaluate a single dose of mRNA-1273.213 100 µg vaccine administered as a single booster dose to adult participants who have previously received 2 doses of any SARS-CoV-2 mRNA authorized vaccine as a primary series. Enrollment of Part E will begin upon completion of enrollment of Part C of the study and will run concurrently with Part D.

Part F

Part F will consist of two cohorts.

Cohort 1 will evaluate 50 µg of the mRNA-1273.529 vaccine administered as a single booster dose to adult participants who have previously received 2 doses of mRNA-1273 as a primary series.

Cohort 2 will evaluate 50 µg of the mRNA-1273.529 vaccine and 50 µg of the mRNA-1273 when administered as a second booster dose to adult participants who have previously received 2 doses of 100 µg mRNA-1273 as a primary series and 1 booster dose of 50 µg mRNA-1273.

Enrollment of the mRNA-1273.529 Cohort 1 will run in parallel with the mRNA-1273.529 in Cohort 2. Enrollment of the 50 µg mRNA-1273 arm in Cohort 2 will begin upon completion of enrollment of the mRNA-1273.529 Cohort 2 arm and may run in parallel with the enrollment of the mRNA-1273.529 Cohort 1 arm.

Part G

Part G will evaluate 50 µg of the mRNA-1273.214 vaccine administered as a second booster dose to adults who have previously received 2 doses of 100 µg mRNA-1273 as a primary series and a single booster dose of 50 µg mRNA-1273. Enrollment of the mRNA-1273.214 50 µg second boost arm will begin upon completion of enrollment of the mRNA-1273 50 µg arm in Cohort 2 of Part F. Enrollment of the mRNA-1273.214 50 µg second boost arm may run in parallel with the enrollment of the mRNA-1273.529 Cohort 1 arm of Part F.

Part H

Part H will evaluate 50 µg of the mRNA-1273.222 vaccine administered as a second booster dose to adults who have previously received 2 doses of 100 µg mRNA-1273 as a primary series and a single booster dose of 50 µg mRNA-1273.

Part J

Part J will evaluate mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg) administered as a booster to adults who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2. Participants will be randomized in a 1:1 ratio to receive either mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg).

Overall, study parts A.1, B, C, and D will assess antibody response of a single booster dose of mRNA vaccines in each study part. Part E will assess a single booster dose in participants who previously received any SARS-CoV-2 mRNA authorized vaccine. Study Part F Cohort 1 will assess whether a single booster dose of the mRNA-1273.529 as the first booster dose elicits a similar or superior antibody response to the B.1.1.529 compared to a single booster dose of mRNA-1273, using an external historical comparator. Study Part F Cohort 2 will assess whether a single booster dose of the mRNA-1273.529 as a second booster dose elicits a similar or superior antibody response to the B.1.1.529 compared to a single booster dose of mRNA-1273 as a second booster dose. Study Part G will assess whether a single booster dose of the mRNA-1273.214 as a second booster dose elicits a similar or superior antibody response to the B.1.1.529 compared to a single booster dose of mRNA-1273 as a second booster dose (Part F, Cohort 2, 50 µg mRNA-1273). Study Part A.2 will evaluate mRNA-1273.214 administered as a second booster dose to participants who rolled over from Part A.1. Study Part H will assess whether a

single booster dose of the mRNA-1273.222 50 µg as a second booster dose elicits a superior antibody response against Omicron BA.4/5 compared to a single booster dose of mRNA-1273 as a second booster dose (Part F, Cohort 2, 50 µg mRNA-1273). Part J will evaluate whether mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg) administered as a booster will elicit antibody response against Omicron subvariants BA.4/BA.5, BQ.1.1, and XBB.1.5 in adults who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2.

Table 2: Study Arm

Study Part	Study Arm	Dose[1]	N
Part A.1	mRNA-1273.211	50 µg	~300
	mRNA-1273.211	100 µg	~584
Part A.2[2]	mRNA-1273.214	50 µg	~300
Part B	mRNA-1273	100 µg	~300
Part C	mRNA-1273.617.2	50 µg	~584
	mRNA-1273.617.2	100 µg	~584
Part D	mRNA-1273.213	50 µg	~584
	mRNA-1273.213	100 µg	~584
Part E	mRNA-1273.213	100 µg	~50-100
Part F (Cohort 1)	mRNA-1273.529	50 µg	~375
Part F (Cohort 2)	mRNA-1273.529	50 µg	~375
	mRNA-1273	50 µg	~375
Part G	mRNA-1273.214	50 µg	~375
Part H	mRNA-1273.222	50 µg	~500
Part J (3rd booster)[3, 4]	mRNA-1273.815	50 µg	~50
	mRNA-1273.231	50 µg	~50

[1] Dose is total mRNA.
[2] Participants rolled over from Part A.1 to Part A.2.
[3] Participants may be rolled over from Part H.
[4] Participants will be randomized in a 1:1 ratio to receive either mRNA-1273.815 or mRNA-1273.231.

4.2. Statistical Hypotheses

Parts A.1, A.2, B, C, and D

There is no hypothesis testing for Parts A.1, A.2, B, C, and D.

Part E

There will be no formal hypothesis testing for Part E. All analyses will be descriptive.

Part F (Cohort 1)

50 µg mRNA-1273.529 as a first booster dose will be assessed with respect to mRNA-1273 as a first booster dose using mRNA-1273-P201 part B 50 µg booster after 100 µg primary series as an external comparator.

For the primary objective on immune response, hypotheses are:

- 50 µg mRNA-1273.529, as a single booster dose, against the variant B.1.1.529 is either non-inferior or superior to the booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.529 against the variant B.1.1.529 at Day 29 compared to mRNA-1273 against the variant B.1.1.529 at Day 29 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.529, as a single booster dose, against the variant B.1.1.529 is non-inferior to the booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the difference in SRR at Day 29 with a non-inferiority margin of 10%.

The primary immunogenicity objective is considered met if non-inferiority against B.1.1.529 (based on GMR and SRR difference) is demonstrated.

Part F (Cohort 2)

50 µg mRNA-1273.529 as a second booster dose will be compared to 50 µg mRNA-1273 as a second booster dose.

For the primary objective on immune response, hypotheses are:

- 50 µg mRNA-1273.529, as a second booster dose, against the variant B.1.1.529 is either non-inferior or superior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.529 against the variant B.1.1.529 at Day 29 compared to mRNA-1273 against the variant B.1.1.529 at Day 29 with a non-inferiority margin of 1.5.

- 50 µg mRNA-1273.529, as a second booster dose, against the variant B.1.1.529 is non-inferior to the booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the difference in SRR at Day 29 with a non-inferiority margin of 10%.

The primary immunogenicity objective is considered met if non-inferiority against B.1.1.529 (based on GMR and SRR difference) is demonstrated.

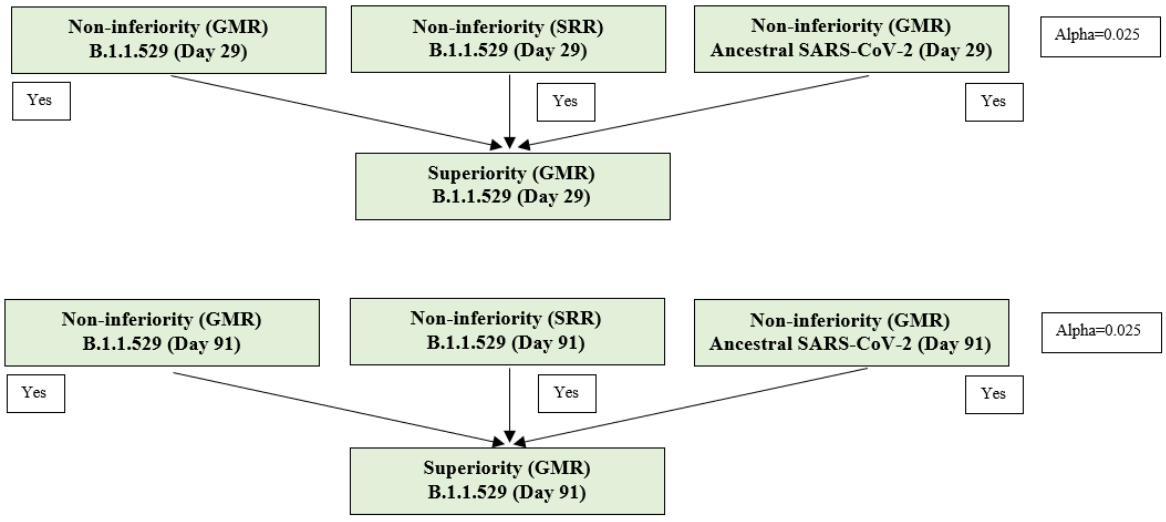
Part G

50 µg mRNA-1273.214 as a second booster dose will be compared to 50 µg mRNA-1273 as the second booster dose (active control arm in Part F, Cohort 2, booster-to-booster comparison for the 2nd booster).

The primary objective on immune response will be tested with 0.025 two-sided alpha each initially allocated to Day 29 and Day 91 respectively. For the primary objective of immune response, an alpha of 0.05 (two-sided) will be allocated to the two time points. Day 29 and Day 91 will each have an alpha of 0.025 (two-sided) for hypotheses testing. If all objectives are met at Day 29, hypotheses at Day 91 can be tested at an alpha of 0.05 (two-sided).

Figure 1 below demonstrates the testing strategy at Day 29 and Day 91.

Figure 1: Statistical Hypotheses Testing Strategy for Part G



Note: If all objectives are met at Day 29, hypotheses at Day 91 can be tested at an alpha of 0.05 (two-sided).

Hypotheses at Day 29:

- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.214 against the variant B.1.1.529 at Day 29 compared to mRNA-1273 against the variant B.1.1.529 at Day 29 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the difference in SRR at Day 29 with a non-inferiority margin of 10%.
- 50 µg mRNA-1273.214, as a second booster dose, against the ancestral SARS-CoV-2 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against the ancestral SARS-CoV-2 based on the GMT ratio of mRNA-1273.214 against the ancestral SARS-CoV-2 at Day 29 compared to mRNA-1273 against the ancestral SARS-CoV-2 at Day 29 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is superior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.214 against the variant B.1.1.529 at Day 29 compared to mRNA-1273 against the variant B.1.1.529 at Day 29. Please note this hypothesis will only be tested when the above 3 hypotheses have been demonstrated.

Hypotheses at Day 91:

- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.214 against the variant B.1.1.529 at Day 91 compared to mRNA-1273 against the variant B.1.1.529 at Day 91 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the difference in SRR at Day 91 with a non-inferiority margin of 10%.

- 50 µg mRNA-1273.214, as a second booster dose, against the ancestral SARS-CoV-2 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against the ancestral SARS-CoV-2 based on the GMT ratio of mRNA-1273.214 against the ancestral SARS-CoV-2 at Day 91 compared to mRNA-1273 against the ancestral SARS-CoV-2 at Day 91 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.214, as a second booster dose, against the variant B.1.1.529 is superior to the second booster dose of (50 µg) mRNA-1273 against B.1.1.529 based on the GMT ratio of mRNA-1273.214 against the variant B.1.1.529 at Day 91 compared to mRNA-1273 against the variant B.1.1.529 at Day 91. Please note this hypothesis will only be tested when the above 3 hypotheses have been demonstrated.

The primary immunogenicity objective is considered met if non-inferiority against B.1.1.529 based on GMR, SRR difference and non-inferiority against the ancestral SARS-CoV-2 based on GMR are demonstrated either at Day 29 or Day 91.

For the key secondary objective, hypotheses are (Day 29 and 91 will each have an alpha of 0.025 (two-sided) for hypotheses testing):

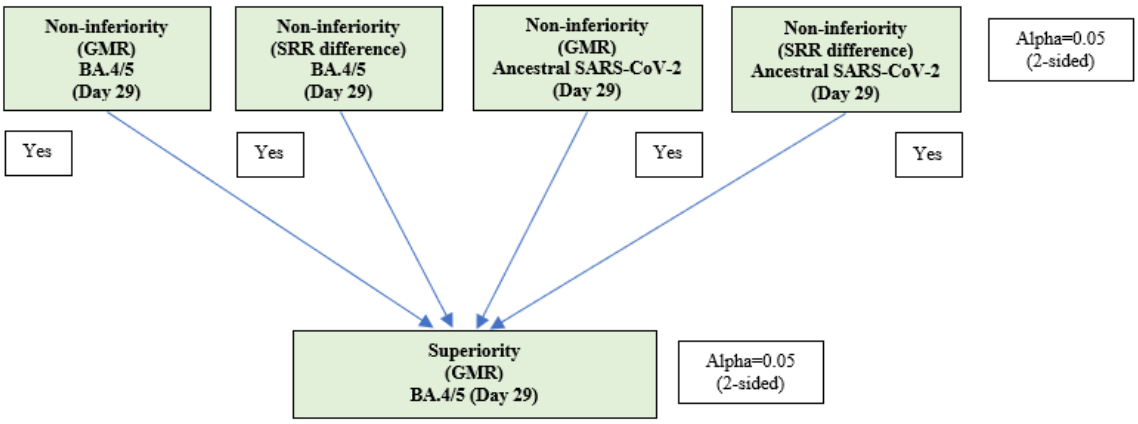
- 50 µg mRNA-1273.214, as a second booster dose, against the ancestral SARS-CoV-2 is non-inferior to the booster dose of (50 µg) mRNA-1273 against the ancestral SARS-CoV-2 based on the difference in SRR at Day 29 with a non-inferiority margin of 10%.
- 50 µg mRNA-1273.214, as a second booster dose, against the ancestral SARS-CoV-2 is non-inferior to the booster dose of (50 µg) mRNA-1273 against the ancestral SARS-CoV-2 based on the difference in SRR at Day 91 with a non-inferiority margin of 10%.

Part H

50 µg mRNA-1273.222 given as a second booster dose will be compared to 50 µg mRNA-1273 given as a second booster dose (in Part F, Cohort 2).

For the primary immunogenicity objective, there are 5 hypotheses to be tested. Figure 2 below demonstrates the testing strategy.

Figure 2: Statistical Hypotheses Testing Strategy for Part H



For the primary immunogenicity objective, the 5 hypotheses to be tested are the following:

- 50 µg mRNA-1273.222, as a second booster dose, against Omicron BA.4/5 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against Omicron BA.4/5 based on the GMT ratio of mRNA-1273.222 against Omicron BA.4/5 at Day 29 compared to mRNA-1273 against Omicron BA.4/5 at Day 29 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.222, as a second booster dose, against Omicron BA.4/5 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against Omicron BA.4/5 based on the difference in SRR at Day 29 with a non-inferiority margin, if
    - the lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/5 at Day 29) is >-5%, then the non-inferiority of mRNA-1273.222 against Omicron BA. 4/5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 5%.
    - the lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/5 at Day 29) is >-10% but ≤ -5%, then non-inferiority of mRNA-1273.222 against Omicron BA. 4/5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 10%.

- 50 µg mRNA-1273.222, as a second booster dose, against the ancestral SARS-CoV-2 D614G is non-inferior to the second booster dose of (50 µg) mRNA-1273 against the ancestral SARS-CoV-2 D614G based on the GMT ratio of mRNA-1273.222 against the ancestral SARS-CoV-2 D614G at Day 29 compared to mRNA-1273 against the ancestral SARS-CoV-2 D614G at Day 29 with a non-inferiority margin of 1.5.
- 50 µg mRNA-1273.222, as a second booster dose, against the ancestral SARS-CoV-2 D614G is non-inferior to the second booster dose of (50 µg) mRNA-1273 against ancestral SARS-CoV-2 D614G based on the difference in SRR at Day 29 with a non-inferiority margin 10%.
- 50 µg mRNA-1273.222, as a second booster dose, against Omicron BA.4/5 is superior to the second booster dose of (50 µg) mRNA-1273 against Omicron BA.4/5 based on the GMT ratio of mRNA-1273.222 against Omicron BA.4/5 at Day 29 compared to mRNA-1273 against Omicron BA.4/5 at Day 29.

Part J

No formal hypothesis testing will be performed for Part J and all safety and immunogenicity analyses will be descriptive.

4.3. Sample Size and Power

Part A.1

With approximately 300 and 584 participants exposed to 50 and 100 µg of mRNA-1273.211, respectively, there is at least 90% probability to observe one participant at each dose level reporting an AE if the true rate of AEs is 1%.

Part A.2

We anticipate approximately 300 participants will be enrolled in Part A.2, there is no statistical hypothesis testing in Part A.2.

Part B

With approximately 300 participants exposed to 100 µg of mRNA-1273, there is at least 90% probability to observe one participant reporting an AE if the true rate of AEs is 1%.

Part C

With approximately 584 participants exposed to each dose of mRNA-1273.617.2, there is at least 90% probability in each group to observe one participant reporting an AE if the true rate of AEs is 1%.

Part D

With approximately 584 participants exposed to each dose of mRNA-1273.213, there is at least 90% probability to observe one participant reporting an AE if the true rate of AEs is 1%.

Part E

The target enrollment of the mRNA-1273.213 in this part of the study is between 50 and 100 participants, with a subset of enrolled participants who previously received Moderna's mRNA-1273 authorized vaccine as a primary series. The sample size for Part E is not driven by statistical assumptions for hypothesis testing.

Part F

mRNA-1273.529 in each cohort will be assessed at a 2-sided type I error rate of 5%.

Cohort 1:

The target enrollment is approximately 375 participants for 50 µg mRNA-1273.529. Assuming 20% of participants will be excluded from the Per-Protocol Immunogenicity SARS-CoV-2 Negative Set (PPIS-Neg), with approximately 300 participants in 50 µg mRNA-1273.529 and 300 participants in 50 µg mRNA-1273 (external comparator, see Section 4.6) in the PPIS-Neg, there is approximately 89% global power for the primary immunogenicity objectives with alpha level of 0.05 (2-sided). The assumptions are: the true GMR (mRNA-1273.529 booster vs. 50 µg mRNA-1273 booster) against the variant (B.1.1.529) is 1.5, the standard deviation of the log-transformed titer is 1.5, and the non-inferiority margin for GMR is 1.5; the true SRR against B.1.1.529 after a single booster dose of 50 µg mRNA-1273.529 is 90% (same assumption for 50 µg mRNA-1273), and non-inferiority margin for SRR difference is 10%.

With approximately 375 participants exposed to 50 µg mRNA-1273.529, there is at least 90% probability in this group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

Cohort 2:

The target enrollment is approximately 750 participants for 50 µg mRNA-1273.529 and 50 µg mRNA-1273 (1:1 ratio). Assuming 20% of participants will be excluded from the PPIS-Neg, with approximately 300 participants each in 50 µg mRNA-1273.529 and 50 µg mRNA-1273 in the Per-Protocol Immunogenicity Set (PPIS) and SARS-CoV-2 negative, there is approximately 89% global power to demonstrate the primary immunogenicity objectives of alpha level of 0.05 (2-sided). The assumptions are: the true GMR (mRNA-1273.529 as the second booster vs 50 µg mRNA-1273 as the second booster) against the variant (B.1.1.529) is 1.5, the standard deviation of the log-transformed titer is 1.5, and the non-inferiority margin for GMR is 1.5; the true SRR against B.1.1.529 after 50 µg mRNA-1273.529 as a second booster dose is 90% (same assumption for 50 µg mRNA-1273), and non-inferiority margin for SRR difference is 10%.

With approximately 375 participants exposed to each group, there is at least 90% probability in each group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

Part G

The target enrollment is approximately 375 participants for 50 µg mRNA1273.214. Hypotheses testing will be performed at Day 29 and Day 91, alpha of 0.025 (2-sided) will be allocated equally to each one of the two time points. Assuming 20% of participants will be excluded from the PPIS-Neg, with approximately 300 participants in 50 µg mRNA1273.214 and 300 participants in 50 µg mRNA-1273 (Part F, Cohort 2-50 µg mRNA-1273) in the PPIS and SARS-CoV-2 negative, there is approximately 71% global power to demonstrate the primary immunogenicity objectives with alpha of 0.025 (2-sided) at each time point. The assumptions are: the true GMR (mRNA-1273.214 second booster vs. 50 µg mRNA-1273 second booster) against the variant (B.1.1.529) is 1.5, the true GMR against ancestral SARS-CoV-2 is 1, the standard deviation of the log-transformed titer is 1.5, and the non-inferiority margin for GMR is 1.5, the true SRR against B.1.1.529 after mRNA-1273.214 as a second booster dose is 90% (same assumption for both 50 µg

mRNA-1273.214 and 50 µg mRNA-1273), and non-inferiority margin for SRR difference is 10%.

With approximately 375 participants exposed to 50 µg mRNA-1273.214, there is at least 90% probability in this group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

Part H

The target enrollment is approximately 500 participants for 50 µg mRNA1273.222. Assuming 40% of participants will be excluded from the PPIS-Neg (due to a SARS-CoV-2 infection pre-booster), with approximately 300 participants in 50 µg mRNA1273.222 and 260 participants in 50 µg mRNA-1273 (Part F, Cohort 2-50 µg mRNA-1273) in the PPIS and SARS-CoV-2 negative, there is approximately 60% power to demonstrate the primary immunogenicity objectives with alpha of 0.05 (2-sided) at Day 29. The assumptions are: the true GMR (mRNA-1273.222 second booster vs. 50 µg mRNA-1273 second booster) against Omicron BA.4/5 is 1.5, GMR (mRNA-1273.222 second booster vs. mRNA-1273 second booster) against ancestral SARS-CoV-2 D614G is 1, the standard deviation of the log-transformed titer is 1.5, and the non-inferiority margin for GMR is 1.5. The true SRR against Omicron BA.4/5 after mRNA-1273.222 as a second booster dose is 95% (same assumption for 50 µg mRNA-1273), and non-inferiority margin for SRR difference against Omicron BA.4/5 is 5%. The true SRR against ancestral SARS-CoV-2 D614G after mRNA-1273.222 as a second booster dose is 95% (same assumption for 50 µg mRNA-1273), and the non-inferiority margin for SRR difference against ancestral SARS-CoV-2 D614G is 10%.

With approximately 500 participants exposed to 50 µg mRNA-1273.222, there is at least 90% probability in this group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

Part J

The sample size for Part J is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of each treatment arm.

The target enrollment is approximately 100 participants who will be randomized in a 1:1 ratio to receive either mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg).

4.4. Randomization

Randomization will be performed for participants in Part J. For Part J, participants will be randomized in a 1:1 ratio to receive one of 2 treatments. Randomization will not be blinded.

4.5. Blinding and Unblinding

Not applicable.

4.6. External Comparator for Part F Cohort 1 - Study mRNA-1273-P201 Part B Subjects

Study mRNA-1273-P201 (P201) Part B, is the Open-Label Interventional Phase of the study, and was prompted by the authorization of a COVID-19 vaccine under an EUA. In Part B, all participants who previously received 1 or 2 injections of mRNA-1273 (50 µg or 100 µg) vaccine were able to receive a single booster dose of mRNA-1273 (50 µg). A total of approximately 150 participants in the P201 50 µg mRNA-1273 booster arm who were primed with 2 doses of 100 µg mRNA-1273 will serve as an external comparator for the P205 Part F 50 µg mRNA-1273.529 arm (Cohort 1).

5. Analysis Sets

The following analysis sets are defined: All Enrolled Set, Full Analysis Set, Per-Protocol Immunogenicity Set, Per-Protocol Immunogenicity Sensitivity Set, Per-Protocol Immunogenicity SARS-CoV-2 Negative Set, Solicited Safety Set, Safety Set, and Per-Protocol Efficacy Set. Definitions are the same across study Parts A (1, 2), B, C, D, E, F, G, H and J when applicable.

5.1. All Enrolled Set

The All Enrolled Set consists of all participants who enrolled in the study for Parts A.1, A.2, B, C, D, E, F, G, H, or were randomized for Part J.

5.2. Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all participants who receive IP.

5.3. Per-Protocol Immunogenicity Set (PPIS)

The Per-Protocol Immunogenicity Set (PPIS) for immunogenicity consists of all P205 participants in the FAS who meet all the criteria listed below, and who were in P201 external comparator who were in the Per-Protocol Set for Part B.

mRNA-1273-P205 participants

a) Received the planned dose of study vaccination per schedule
b) For Parts A.1, A.2, B, C, D, F, G, H: had pre-booster and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data; for Part J: had pre-booster and Day 15 neutralizing antibody data

- Part A.1: against B.1.351 variant
- Part A.2: against B.1.1.529 variant
- Part B: against ancestral SARS-CoV-2
- Part C: against B.1.617.2 variant
- Part D: against B.1.351 variant and B.1.617.2 variant
- Part F (Cohort 1 and Cohort 2): against B.1.1.529 variant
- Part G: against B.1.1.529 variant
- Part H: against BA.4/5 variant
- Part J: against XBB.1.5 variant

c) Had no major protocol deviations that impact key or critical data
d) Had no previous HIV infection

mRNA-1273-P201 external comparator

Consists of P201B participants after 100 µg primary series who were in Per-Protocol Set for Part B (please refer to P201 SAP version 5.0 Section 5.6 for details).

The PPIS will be used as the primary analysis set for analyses of immunogenicity for Parts A.1, B, C, D, and J, Full Analysis Set will be used for Part E binding antibody descriptive summary.

5.4. Per-Protocol (PP) Immunogenicity Sensitivity Set

For Parts A.1, A.2, B, C, D, F, G, H, the PP Immunogenicity Sensitivity Set for immunogenicity may be used for sensitivity analysis and will consist of participants who meet all requirements for the PPIS with the exception of the time window for Day 29 neutralizing antibody data.

mRNA-1273-P205 participants

a) Received the planned dose of study vaccination per schedule
b) Had pre-booster and Day 29
- Part A.1: against B.1.351 variant
- Part A.2: against B.1.1.529 variant
- Part B: against ancestral SARS-CoV-2
- Part C: against B.1.617.2 variant
- Part D: against B.1.351 variant and B.1.617.2 variant
- Part F (Cohort 1 and Cohort 2): against B.1.1.529 variant
- Part G: against B.1.1.529 variant
- Part H: against BA.4/5 variant

c) Had no major protocol deviations that impact key or critical data
d) Had no previous HIV infection

5.5. Per-Protocol Immunogenicity SARS-CoV-2 Negative Set (PPIS-Neg)

The PPIS-Neg Set consists of P205 participants who meet all requirements for the PPIS and have no serologic or virologic evidence of SARS-CoV-2 infection at baseline and P201B participants who were in the Per-Protocol Set for Part B.

mRNA-1273-P205 participants

a) Received the planned dose of study vaccination per schedule

b) For Parts A.1, A.2, B, C, D, F, G, H: had pre-booster and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data; for Part J: had pre-booster and Day 15 neutralizing antibody data

- Part A.1: against B.1.351 variant
- Part A.2: against B.1.1.529 variant
- Part B: against ancestral SARS-CoV-2
- Part C: against B.1.617.2 variant
- Part D: against B.1.351 variant and B.1.617.2 variant
- Part F (Cohort 1 and Cohort 2): against B.1.1.529 variant
- Part G: against B.1.1.529 variant
- Part H: against BA.4/5 variant
- Part J: against XBB.1.5 variant

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

d) Had no previous HIV infection

e) Have no serologic or virologic evidence of SARS-CoV-2 infection at baseline (ie, who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid)

mRNA-1273-P201B external comparator

Consists of P201B participants after 100 µg primary series who were in Per-Protocol Set for Part B (please refer to P201 SAP version 5.0 Section 5.6 for details).

The PPIS-Neg Set will used as the primary analysis set for analyses of immunogenicity for Parts A.2, F (Cohort 1), F (Cohort 2), G, and H.

5.6. Solicited Safety Set

The Solicited Safety Set consists of all participants who receive IP and contribute any solicited AR data.

The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the study arm corresponding to the dose of IP that they actually received.

5.7. Safety Set

The Safety Set consists of all participants who receive IP.

The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the study arm corresponding to the dose of IP that they actually received.

5.8. Per-Protocol (PP) Efficacy Set

The PP Efficacy Set consists of all participants in the FAS who received the planned dose of study vaccination, who are SARS-CoV-2 negative pre-booster (ie, have a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid pre-booster), and have no major protocol deviations that impact key or critical data.

The PP Efficacy Set will be used as the primary analysis set for analyses of efficacy unless otherwise specified.

6. Statistical Analysis

6.1. General Considerations

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

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the dose of IP in this study. Pre-booster and baseline are used interchangeably for the study arms in P205. For immunogenicity tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the dose 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 in order to draw attention to the non-zero counts. “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the corresponding group, unless otherwise specified.

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 at pre-booster 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-C oV-2 assay) on or before Day 1.

Negative status at pre-booster is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti- SARS-C oV-2 assay) on or before Day 1.

Study day relative to the injection will be calculated as follows:

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

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

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

The following **analysis periods for safety analyses** will be used:

- 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 solicited ARs, 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 the analysis as follows:

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

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

Incomplete/missing data:

- Imputation rules for missing or incomplete days of 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 (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ for the calculation of summary values. If the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary if actual values are not available.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups

- Part A.1: 50 µg of mRNA-1273.211 and 100 µg of mRNA-1273.211
- Part A.2: 50 µg of mRNA-1273.214
- Part B: 100 µg of mRNA-1273
- Part C: 50 µg of mRNA-1273.617.2 and 100 µg of mRNA-1273.617.2
- Part D: 50 µg of mRNA-1273.213 and 100 µg of mRNA-1273.213
- Part E: 100 µg of mRNA-1273.213
- Part F Cohort 1: 50 µg of mRNA-1273.529
- Part F Cohort 2: 50 µg of mRNA-1273.529 and 50 µg of mRNA-1273
- Part G: 50 µg of mRNA-1273.214
- Part H: 50 µg of mRNA-1273.222
- Part J: 50 µg of mRNA-1273.815 and 50 µg of mRNA-1273.231

External comparator

- 50 µg of mRNA-1273 (booster arm primed with 2 doses of 100 µg mRNA-1273 from Study mRNA-1273-P201 used as an external comparator for P205 Part F Cohort 1).

Subgroup Analysis

Immunogenicity will be assessed in the following subgroups:

- Age (18 to <65, and ≥65 years)

- Sex (female, male)
- Pre-booster SARS-CoV-2 status (negative, positive) if there is enough of pre-booster positives
- Race (White, Black or African American, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Safety may be assessed for the same subgroups.

Subgroup analyses may not be performed for Part J due to small sample size.

Analyses Approach

There are multiple parts in P205, all analyses and data summaries/displays will be provided by study arm for each study part using appropriate analysis population.

Subjects Received Off-study COVID-19 Vaccine

If a participant received off-study COVID-19 vaccine, the participant's immune response and effectiveness data will be censored at the earlier date of date of off-study COVID-19 vaccine, or date of last observed in study.

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

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized as defined in Section 6.1 based on:

- Full Analysis Set
- Per-Protocol Immunogenicity Set
- Per-Protocol Immunogenicity Sensitivity Set
- Per Protocol Immunogenicity SARS-CoV-2 Negative Set
- Solicited Safety Set
- Safety Set
- Per-Protocol Efficacy Set

The percentage will be based on the number of subjects in the All Enrolled Set.

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

- Received the dose of IP
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

This study treatment only consists of a 1-dose booster, thus discontinuation from study treatment is not applicable to this study. A subject who completed 12 months of follow up after the injection is considered to have completed the study for study parts A.1, B, C, D, E, F, and G. A subject who completed 6 months of follow up after the injection is considered to have completed the study for study parts A.2, H and J.

A subject disposition listing for participants who discontinued the study early will be provided, including informed consent, subjects who were vaccinated, subjects who completed the study, subjects discontinued from the study, with reasons for discontinuation.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of subjects will be provided for categorical variables such as age group (18 to <65, and ≥65 years), gender, race, ethnicity, pre-booster SARS-CoV-2 status, time duration from completion of primary series to booster dose, time duration from first to second booster dose (if applicable), and time duration from second to third booster dose (if applicable). The summaries will be provided based on the Safety Set and Per-Protocol Immunogenicity Set. If the subjects in two or more analysis sets are identical, only one table will be provided for such analysis sets.

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. SOCs will be displayed in internationally agreed

order and, within each SOC, PTs will be displayed in alphabetical order for first booster, in descending order of frequency based on the mRNA-1273 50 µg group then alphabetically for second booster, and in descending order of frequency based on the mRNA-1273.231 50 µg group then alphabetically for third booster.

6.2.4. Prior and Concomitant Medications

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

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 alphabetical order for first booster, in descending order of frequency based on the mRNA-1273 50 µg group then alphabetically for second booster, and in descending order of frequency based on the mRNA-1273.231 50 µg group then alphabetically for third booster.

Medications taken to prevent pain or fever will be collected on eDiary and summaries will be provided based on the Solicited Safety Set as defined in Section 6.1, including within 7 days after injection, beyond 7 days after injection and after injection.

6.2.5. Study Exposure

Summary of study exposure will be summarized.

Study duration, defined as time on study from the injection/booster to study discontinuation, study completion, or last contact date, whichever occurs earlier, will be summarized.

6.2.6. Major Protocol Deviations

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

The number and percentage of the subjects with each major protocol deviation type will be provided as defined in Section 6.1 based on the FAS.

Major protocol deviations will be presented in a listing.

Select major protocol deviations are deemed to impact critical data and lead to exclusion from the Per-Protocol Immunogenicity Set or Per-Protocol Efficacy Set. Number of subjects with such major protocol deviations leading to exclusion from the PP Sets will be summarized.

6.3. Safety Analysis

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

Safety analyses will be based on the Safety Set, except that the Solicited Safety Set will be used for analyses of solicited AR.

6.3.1. Adverse Events

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

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

Overview of unsolicited AEs will be summarized by stage, up to 28 days after vaccination and throughout the study (see 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 subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in alphabetical order for first booster, in descending order of frequency based on the mRNA-1273 50 µg group then alphabetically for second booster, and in descending order of frequency based on the mRNA-1273.231 50 µg group then alphabetically for third booster. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to

the highest severity in the summaries by severity, if subjects reported multiple events under the same SOC and/or PT.

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

6.3.1.1. Incidence of Adverse Events

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

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any unsolicited AESIs
- Any unsolicited non-serious TEAEs
- Any unsolicited severe non-serious TEAEs

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

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

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event), up to 28 days after vaccination. Select TEAEs that will be collected throughout the study will also be summarized throughout the study when applicable:

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

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

6.3.2. Solicited Adverse Reactions

6.3.2.1. Analysis of Solicited Adverse Reactions

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

Analyses of solicited ARs will be provided based on the Solicited 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 subjects who reported each individual solicited local AR and solicited systemic AR during the 7-day follow-up period after the injection 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 subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR.

  ii. The number and percentage of subjects who reported each individual solicited local AR and 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 solicited AR is defined as the time point after the injection at which the respective solicited AR first occurred.

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

  i. Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

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

  i. The number and percentage of subjects who reported each individual solicited local AR and 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 subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR persisting beyond 7 days after injection.

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

  i. The incidence for each individual solicited local AR and solicited systemic AR 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 each individual solicited local AR and solicited systemic AR with onset day after the 7-day follow-up period after the injection (i.e., after Day 7) will be summarized descriptively.

  iii. The number of days reporting each individual solicited local AR and solicited systemic AR 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 subjects 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 on Day 1. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. 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 table in the protocol with pre- and post-dosing on the day of injection (Day 1) only. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be provided in the listing.

6.4. Immunogenicity Analysis

The primary analysis population for immunogenicity will be the PPIS for Parts A.1, B, C, D, and J, FAS for Part E, and the PPIS-Neg will be the primary analysis population for immunogenicity analyses for Parts A.2, F (Cohort 1), F (Cohort 2), G, and H. Refer to Appendix E for a summary of immunogenicity endpoints.

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

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

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

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

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

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

6.4.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE table in the protocol. Immunogenicity assessments that were tested and applicable for analysis are displayed in Table 3 for neutralizing antibody assessment. Binding antibody were also assessed at the same timepoints.

Table 3: Neutralizing antibody assessments tested by part, dose, time point, and variant

	Dose	D1	D15	D29	D91	D181	D366
Part A.1	**.211 50 µg**	D614G/ .351/ .617/ BA.1		D614G/ .351/ .617/ BA.1	N/A	D614G/ .351/ .617/ BA.1	Not done
	.211 100 µg	D614G/ .351/ .617		D614G/ .351	N/A	D614G/ .351	Not done
Part B	**1273 100 µg**	D614G/ .617/ .351		D614G/ .617/ .351	N/A	Not done	Not done
Part C	**.617 50 µg**	D614G/ .617		D614G/ .617	N/A	Not done	Not done
	.617 100 µg	D614G/ .617		D614G/ .617	N/A	Not done	Not done
Part D	**.213 50 µg**	D614G/ .617/ .351		D614G/ .617/ .351	N/A	Not done	Not done
	.213 100 µg	D614G/ .617/ .351		D614G/ .617/ .351	N/A	Not done	Not done
Part E	**.213 100 µg**	D614G		D614G	N/A	Not done	Not done

Part F	**.529 Booster 1 50 µg**	D614G/ BA.1		D614G/ BA.1	Not done	Not done	Not done
	.529 Booster 2 50 µg (4th dose)	D614G/ BA.1		D614G/ BA.1	Not done	Not done	Not done
	1273 50 µg	D614G/ BA.1		D614G/ BA.1	D614G/ BA.1	D614G/ BA.1	D614G/ BA.1
Part G	**.214 50 µg**	D614G/ BA.1		D614G/ BA.1	D614G/ BA.1	D614G/ BA.1	D614G/ BA.1
Part H	**.222 50 µg**	D614G/ BA4.5		D614G/ BA4.5	Not done	D614G/ BA4.5	N/A
Part A.2	**.214 50 µg**	D614G/ BA.1/ .351		D614G/ BA.1/ .351	Not done	D614G/ BA.1/ .351	N/A
Part J	**.231/.815 50 µg**	D614G/ BQ1.1/ BA4.5/ XBB1.5	D614G/ BQ1.1/ BA4.5/ XBB1.5	D614G/ BQ1.1/ BA4.5/ XBB1.5	Not done	D614G/ BQ1.1/ BA4.5/ XBB1.5	N/A

6.4.2. Selecting P201B Subjects as External Comparator

Please refer to Section 4.6 regarding the selection of P201B participants as an external comparator whose immunogenicity will be compared with that for 50 µg mRNA-1273.529 arm (Part F, Cohort 1).

6.4.3. Primary Analysis of Antibody-Mediated Immunogenicity Endpoints

Part A.2

For Part A.2 participants, Day 29 and Day 181 immune response after mRNA-1273.214 (50 µg) as a second booster dose will be compared with their own Day 29 and Day 181 immune response of mRNA-1273.211 (50 µg) received as the first booster dose. GMT ratios will be calculated by back transforming the mean of paired differences of antibody titer data on the logarithmic scale between Day 29 and Day 181 post mRNA-1273.214 and Day 29 and Day 181 of antibody titer data post mRNA-1273.211. CIs for the GMT ratio will be based on t-distribution of the log-transformed values then back transformed to the original scale for presentation. Seroresponse rates at Day 29 and Day 181 post mRNA-1273.214 will be compared with their seroresponse rates at Day 29 and Day 181 post

mRNA-1273.211. The difference in seroresponse rates and its corresponding 95% CI based on adjusted Wald method will be provided.

Part F Cohort 1

Primary analysis set for immunogenicity objectives will be based on PPIS-Neg.

For the primary objective on immune response for a first booster dose of 50 µg mRNA-1273.529, see Section 4.2. An analysis of covariance (ANCOVA) model will be performed to assess the difference in immune response between mRNA-1273.529 and mRNA-1273 (P201B 50 µg booster after 100 µg primary series) as the first booster dose. For immune response against the B.1.1.529 strain, in the ANCOVA model, 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 (< 65, ≥ 65 years) and pre-booster antibody titer level if applicable; the model may also be adjusted for other characteristics.

The GMT will be estimated by the GLSM from the model and its corresponding 95% 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 and the corresponding 95% CIs will be provided. The 95% 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.

The number and percentage (rate) of participants achieving seroresponse at Day 29 will be summarized with 95% CI calculated using the Clopper-Pearson method for each group. The difference of SRR between mRNA-1273.529 and mRNA-1273 will be calculated with 95% CI based on stratified Miettinen-Nurminen method adjusted for age group. The non-inferiority in SRR of mRNA-1273.529 compared to mRNA-1273 will be considered demonstrated if the lower bound of the 95% of the SRR difference is > -10% based on the non-inferiority margin of 10%.

The primary immunogenicity objective (against the variant B.1.1.529) is considered met if non-inferiority is demonstrated based on GMR and SRR difference, specifically:

- If the lower bound of the 95% CI of the GMT ratio between mRNA1273.529 against the variant (B.1.1.529) at Day 29 as compared to 50 µg mRNA1273 against B.1.1.529 at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.

- The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.529 against the variant B.1.1.529 at Day 29 - 50 µg mRNA-1273 against B.1.1.529) is > -10%.
- If non-inferiority is demonstrated, the lower bound of 95% CI of the GMT ratio will be compared to 1, if it's greater than 1, then superiority is demonstrated.

A supportive analysis for the primary immunogenicity endpoints may also be performed using Per-Protocol Immunogenicity Set. For immune response against the B.1.1.529 strain, in the ANCOVA model, 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 (< 65, ≥ 65 years), pre-booster SARS-CoV-2 status, and pre-booster titer if applicable; the model may also be adjusted for other characteristics. The difference of SRR between mRNA-1273.529 and mRNA-1273 will be calculated with 95% CI based on stratified Miettinen-Nurminen method adjusted for pre-booster SARS-CoV-2 status and age group.

Part F Cohort 2

Primary analysis set for immunogenicity objectives will be based on PPIS-Neg.

50 µg mRNA-1273.529 as the second booster dose will be compared to 50 µg mRNA-1273 as the second booster dose. For the primary objective on immune response for a second booster dose of 50 µg mRNA-1273.529, see Section 4.2. The same analysis methods described for Part F Cohort 1 will be used for the primary immunogenicity objective for Part F Cohort 2.

The primary immunogenicity objective (against the B.1.1.529) is considered met if non-inferiority is demonstrated based on GMR and SRR difference, specifically:

- The lower bound of the 95% CI of the GMT ratio between mRNA1273.529 against the variant (B.1.1.529) at Day 29 as compared to 50 µg mRNA-1273 against B.1.1.529 at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.
- The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.529 against the variant B.1.1.529 at Day 29 - 50 µg mRNA-1273 against B.1.1.529 at Day 29) is >-10%.

- If non-inferiority is demonstrated (based on GMT ratio and SRR difference), the lower bound of 95% CI of GMT ratio will be compared to 1, if it's greater than 1, then superiority is demonstrated.

Analyses for the primary immunogenicity endpoints may also be performed using Per-Protocol Immunogenicity Set similar to Part F Cohort 1.

Part G

Primary analysis set for immunogenicity objectives will be based on PPIS-Neg.

50 µg mRNA-1273.214 as the second booster dose will be compared to 50 µg mRNA-1273 as the second booster dose (active control arm in Part F, Cohort 2). For the primary objective on immune response for a second booster dose of 50 µg mRNA-1273.214, hypotheses are to be tested at Day 29 and Day 91 (see Section 4.2). For the primary objective of immune response, an alpha of 0.05 (two-sided) will be allocated to the two time points. Day 29 and Day 91 will each have an alpha of 0.025 (two-sided) for hypotheses testing. The analyses method described in Part F Cohort 1 will be used for Part G.

The primary immunogenicity objective is considered met if non-inferiority against B.1.1.529 based on GMR and SRR difference and non-inferiority against the ancestral SARS-CoV-2 based on GMR are demonstrated based on GMR at Day 29 or Day 91.

Day 29: alpha = 0.025 (2-sided)

- The lower bound of the 97.5% CI of the GMT ratio between mRNA-1273.214 against the variant (B.1.1.529) at Day 29 as compared to 50 µg mRNA-1273 against B.1.1.529 at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.
- The lower bound of the 97.5% CI of the SRR difference (50 µg mRNA-1273.214 against the variant B.1.1.529 at Day 29 - 50 µg mRNA-1273 against B.1.1.529 at Day 29) is >-10%.
- The lower bound of the 97.5% CI of the GMT ratio between mRNA-1273.214 against ancestral SARS-CoV-2 at Day 29 as compared to 50 µg mRNA-1273 against ancestral SARS-CoV-2 at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.

- If non-inferiority is demonstrated for both B.1.1.529 (based on GMR and SRR) and ancestral SARS-CoV-2 (based on GMR), the lower bound of 97.5% CI of GMR will be compared to 1, if it's greater than 1, then superiority against B.1.1.529 is demonstrated.

Analyses for the primary immunogenicity endpoints may also be performed using Per-Protocol Immunogenicity Set.

Day 91: alpha=0.025 (2-sided)

Hypotheses testing at Day 91 will be performed in the same manner, first test two non-inferiority hypotheses (two against the B.1.1.529 strain and one against ancestral SARS-CoV-2) at alpha of 0.025 level (two-sided). Once non-inferiority is demonstrated for both B.1.1529 and ancestral SARS-CoV-2, then superiority testing against the B.1.1.529 at alpha of 0.025 level (two-sided) will be performed.

For the key secondary objective, hypotheses to be tested (Day 29 and Day 91 each with alpha level of 0.025, 2-sided) are described in Section 4.2. If the lower bound of the 97.5% CI of the SRR difference (50 µg mRNA-1273.214 against the ancestral SARS-CoV-2 - 50 µg mRNA-1273 against ancestral SARS-CoV-2) is >-10% at Day 29 or Day 91, then key secondary objective will be considered met.

In the event that an early assessment of the 1273.214 data is needed due to public health concerns, a two-staged approach will be used. Specifically, a subset of participants' (ie, 50 first enrolled participants) serum samples will first be tested against ancestral SARS-CoV-2 and various VOCs. For the Day 29 and Day 91 immunogenicity analyses, all participants' immune data will be used in the formal analysis to evaluate the primary immunogenicity objective.

Part H

Primary analysis set for immunogenicity objectives will be based on PPIS-Neg.

50 µg mRNA-1273.222 as the second booster dose will be compared to 50 µg mRNA-1273 as the second booster dose (active control arm in Part F, Cohort 2).

Study Part H was enrolled in August 2022 and Part F 50 µg mRNA-1273 was enrolled in February 2022, baseline and demographic characteristics will be examined between the two study parts before comparing immunogenicity data.

An analysis of covariance (ANCOVA) model will be performed to assess the difference in immune response between mRNA-1273.222 and mRNA-1273. In the ANCOVA model, antibody titers at Day 29 post-booster against the Omicron BA. 4/5 strain will be a dependent variable, and a group variable (mRNA-1273.222 and mRNA-1273) will be the fixed effect, adjusting for age, pre-booster antibody titer level if applicable; the model may also be adjusted for other characteristics. Age group (≥65, <65 years) or age as continuous variable may be considered in the ANCOVA model.

The GMT will be estimated by the GLSM from the model and its corresponding 95% will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.222 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 95% CIs will be provided. The 95% CI for GMR will be used to assess the between group difference in immune response against the BA. 4/5 strain for mRNA-1273.222 at Day 29 compared to the mRNA-1273.

The number and percentage (rate) of participants achieving seroresponse at Day 29 will be summarized with 95% CI calculated using the Clopper-Pearson method for each group. The difference of SRR between mRNA-1273.222 and mRNA-1273 will be calculated with 95% CI based on stratified Miettinen-Nurminen (MN) method adjusted for age group.

A supportive analysis for the primary immunogenicity endpoints may also be performed using Per-Protocol Immunogenicity Set. For immune response against the BA.4/5 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the BA.4/5 strain will be a dependent variable, and a group variable (mRNA-1273.222 and mRNA-1273) will be the fixed effect, adjusting for age, pre-booster SARS-CoV-2 status, pre-booster titer if applicable; the model may also be adjusted for other characteristics. Age group (≥65, <65 years) or age as continuous variable may be considered in the ANCOVA model. The difference of SRR between mRNA-1273.222 and mRNA-1273 will be calculated with 95% CI based on stratified Miettinen-Nurminen method adjusted for pre-booster SARS-CoV-2 status and age group.

The primary immunogenicity objective (against BA.4/5 and ancestral SARS-CoV-2 D614G) is considered met if non-inferiority is demonstrated based on GMR and SRR difference, specifically:

- The lower bound of the 95% CI of the GMT ratio between mRNA1273.222 against Omicron BA.4/5 at Day 29 as compared to 50 µg mRNA-1273 against Omicron BA.4/5 at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.
- 50 µg mRNA-1273.222, as a second booster dose, against Omicron BA.4/5 is non-inferior to the second booster dose of (50 µg) mRNA-1273 against Omicron BA.4/5 based on the difference in SRR at Day 29 based on a non-inferiority boundary, if:
    - The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/5 at Day 29) is >-5%, then the non-inferiority of mRNA-1273.222 against Omicron BA. 4/5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 5%.
    - The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/5 at Day 29) is >-10% but ≤-5%, then non-inferiority of mRNA-1273.222 against Omicron BA. 4/5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 10%.
- The lower bound of the 95% CI of the GMT ratio between mRNA1273.222 against the ancestral SARS-CoV-2 D614G at Day 29 as compared to 50 µg mRNA-1273 against the ancestral SARS-CoV-2 D614G at Day 29 is > 0.667 based on the non-inferiority margin of 1.5.
- The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against the ancestral SARS-CoV-2 D614G at Day 29 - 50 µg mRNA-1273 against ancestral SARS-CoV-2 D614G at Day 29) is >-10%.
- If non-inferiority is demonstrated (against Omicron BA. 4/5 and ancestral SARS-CoV-2 D614G based on GMT ratio and SRR difference with a NI margin of 10%), the lower bound of 95% CI of GMT ratio will be compared to 1, if it's greater than 1, then superiority is demonstrated.

Part J

No formal hypothesis testing will be performed for Part J and all safety and immunogenicity analyses will be descriptive.

The primary immunogenicity objective will be assessed using the Per-Protocol Immunogenicity Set. Descriptive comparisons on immunogenicity response between the mRNA-1273.815 and mRNA-1273.231 treatment arms will be performed.

6.4.4. Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints

For Part E, immune response to ancestral SARS-CoV-2 and circulating variants for concern after a single booster dose of 100 µg mRNA-1273.213 will be summarized descriptively.

The mixed effect model repeated measure (MMRM) will be used to analyze all post-booster measures for between booster comparisons (Part G, and Part H) when analyzing immunogenicity data at Month 6 and Month 12 (if applicable), the model will include treatment group, analysis visit, treatment by visit interaction, and adjusting for age groups and pre-booster titer levels, and pre-booster SARS-CoV-2 status when applicable (i.e. using Per-Protocol Immunogenicity Set). An unstructured covariance structure will be used to model the within-participant errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If the model does not converge, a compound symmetry covariance structure will be used. 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 (ratio of GMTs) will be estimated from the model and the corresponding 95% CI will be provided at each post-boost timepoint.

6.4.5. Exploratory Analysis of Antibody-Mediated Immunogenicity Endpoints

For each booster arm, the following evaluations will be performed at each time point at which blood samples are tested for immunogenicity (unless otherwise specified).

- In relation to the immune response of each booster arm to other SARS-CoV-2 viral variants, the GMT, geometric mean fold rise (GMFR) and seroresponse rate will be calculated at the time points where the immune response is assessed for such variants.
- For each antibody of interest, the GMT or level with corresponding 95% CI at each 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.

- For each antibody of interest 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.
- For each antibody of interest, the proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 from baseline at each post-injection time point will be tabulated with 95% CI calculated using the Clopper-Pearson method.
- Seroresponse rate of each booster arm against the ancestral SARS-CoV-2 and variants, defined as the percentage of participants achieving seroresponse against the ancestral SARS-CoV-2 strain and variants respectively, will be provided with the 95% CI calculated using the Clopper-Pearson method.

6.4.6. Sensitivity Analysis

Sensitivity analysis for the immunogenicity endpoints may be performed with the same methods described above based on the PP Immunogenicity Sensitivity Set.

Sensitivity analysis may be performed for the primary immunogenicity endpoints by excluding all records after SARS-CoV-2 infection.

Additional sensitivity analysis may be performed to assess robustness of the primary immunogenicity analysis results for GMR if more than 10% immunogenicity data are missing at Day 29 or Day 91 (Part G) in the Per-Protocol Immunogenicity Set. Multiple imputation will be used to impute for missing antibody titer data. Following steps outline multiple imputation process and subsequent analysis.

Step 1: We will assume antibody titer data follows a log normal distribution.

- Markov Chain Monte Carlo (MCMC) will be used for imputation, imputation model will include treatment group, pre-booster baseline titer, age group, Day 29/ Day 91 (when applicable) titer data in log scale (with a base of 10). Each missing data point will be filled with a set of imputed values.

Step 2: Generate a set of datasets with imputed antibody titer values.

Step 3: Each complete dataset will be analyzed using ANCOVA model with treatment group as a fixed effect, adjusting for pre-booster baseline tier, and age group. Each model will estimate GMR (between treatment group comparison) and standard error in Log 10 scale.

Step 4: The results from these analyses will be combined into a single estimate using Rubin's (1987) method, the combined estimate will be transformed back to original scale for presentation.

6.4.7. Seroresponse

Seroresponse is defined as ≥ 4*LLOQ for those with baseline <LLOQ; ≥ 4-foldrise for those with baseline ≥ LLOQ.

Seroresponse will be derived based on two types of baselines:

1) Pre-vaccination (Pre-Dose 1 of the primary series)
2) Pre-booster baseline

Both definitions will be used when comparing seroresponse rate for all study parts. Seroresponse based on change (fold rise) from pre-dose 1 of the primary series would be considered the primary approach of seroresponse.

For subjects without pre-Dose 1 antibody titer information, seroresponse is defined as ≥ 4*LLOQ for subjects with negative SARS-CoV-2 status at their pre-dose 1 of primary series, and these subjects antibody titer will be deemed <LLOQ at pre-dose 1 of primary series.

- For subjects who are without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status will be used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

6.5. Efficacy Analysis

Vaccine efficacy will not be formally assessed in this trial but active surveillance for COVID-19 and SARS-CoV-2 infection through weekly contact and blood draws (see SoE, table in the protocol), will be performed.

Pre-booster SARS-CoV-2 status is described in Section 6.1. Pre-booster SARS-CoV-2 status, the serology test results based on Roche Elecsys assay pre-booster, the RT-PCR test results pre-booster will be summarized.

In this study, the serology test results based on Roche Elecsys assay 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 PP Efficacy Set, unless otherwise specified. FAS may be used for supportive analyses. All results will be summarized by study arm for each study part.

6.5.1. Endpoint Definition/Derivation

6.5.1.1. Derivation of SARS-CoV-2 Infection

SARS-CoV-2 infection is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection. SARS-CoV-2 infection will be defined in participants by either:

- Participants with negative SARS-CoV-2 status at baseline and that becomes serology positive (as measured by *Roche Elecsys*) post baseline, OR
- Positive RT-PCR post baseline.

During the analysis, documented infection is counted starting 14 days after the dose of IP.

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 injection + 1.

Cases will be counted starting 14 days after the injection, i.e. date of documented infection - Date of the injection ≥ 14.

SARS-CoV-2 infection cases will also be summarized based on tests performed at least 14 days after the dose of IP.

6.5.1.2.Derivation of Asymptomatic SARS-CoV-2 Infection

This is an exploratory efficacy endpoint: the incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR of nasal swabs and/or serology tests obtained at post-baseline study visits counted starting 14 days after the injection.

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

- Absent of COVID-19 symptoms

  AND at least one from below:

  - Participants with negative SARS-CoV-2 status at baseline and becomes positive (serology test result based on bAb specific to SARS-CoV-2 nucleocapsid protein) post baseline, when blood samples for immunogenicity are collected, or
  - Positive RT-PCR test 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 , 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 injection + 1.

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

This is an exploratory efficacy endpoint: the incidence of the first occurrence of symptomatic SARS-CoV-2 infection measured by RT-PCR of nasal swabs counted starting 14 days after the injection. Surveillance for COVID-19 symptoms will be conducted via weekly contact and blood draw. Subjects reporting COVID-19 symptoms will be arranged an illness visit to collect an NP swab.

Two definitions of symptomatic SARS-CoV-2 Infection, COVID-19, will be evaluated:

1. Primary case definition per the P301 (COVE) study: Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results as described in Table 4-1.
2. Secondary case definition based on CDC criteria: Cases are defined as participants with symptomatic disease based on the criteria defined by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html).

Table 4-1: Derivation of primary case definition of COVID-19

COVID-19 (per the P301 COVE study)	
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 4-2: Derivation for secondary case definition of COVID-19

COVID-19 (CDC criteria)	
Post-baseline PCR results	Positive, **AND**
Systemic and Respiratory Symptoms	at least ONE of the following **systemic or respiratory symptoms**: Fever (≥ 38ºC/≥ 100.4º F), chills, cough, shortness of breath and/or difficulty

	breathing, fatigue, muscle and/or body aches (not related to exercise), headache, new loss of taste/smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhea.

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

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

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

Cases will be counted starting 14 days after the injection, i.e. date of documented COVID-19 - Date of the injection ≥ 14.

6.5.2. Analysis Method

The number and percentage of subjects who had each type of event (ie, an asymptomatic or a symptomatic SARS-CoV-2 infection) will be summarized in the PP Efficacy Set.

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

Person-time is defined as the total time from injection date to the date of event, last date of study participation, or censoring time, whichever is earlier.

6.5.3. Sensitivity Analysis

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

6.5.4. SARS-CoV-2 Exposure and Symptoms

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

6.5.5. Sequencing

For breakthrough infections with available sequencing data, summary of infections by variants will be provided..

6.6. Interim Analysis

The interim analysis will be conducted on safety and immunogenicity data collected through Day 15 or Day 29. The interim analysis may be performed either after all subjects in Part A.1, Part A.2, Part B, Part C, Part D, Part F, Part G, Part H or Part J have completed their Day 15 or Day 29 visit assessments and/or subsequent timepoint visits (eg, Day 91 for Parts F, G, H and J) or combined after the last subject of each study part (Parts A.1, A.2, B, C, D, F, G, H, or J) dose arm, or pre-specified subset of dose arm has completed their Day 15 or Day 29 visit assessments.

6.7. Data Safety Monitoring Board

Not applicable.

6.8. Final Analysis

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings. The final CSR will include full analyses of all safety and immunogenicity through Day 366 (Month 12) for Parts A.1. B, C, D, E, F, and G and through Day 181 (Month 6) for Parts A.2, H and J.

7. References

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8. List of Appendices

8.1. Appendix A. Standards for Safety and Immunogenicity Variable Display in TFLs

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

Antibody titer GMTs, and GMFRs will be presented to 1 decimal place, GMT ratio will be presented to three decimal places.

Categorical Variables: Percentages will be presented to 1 decimal place.

8.2. Appendix B. Analysis Visit Windows for Safety and Immunogenicity Analysis

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

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

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Tables 5 and 6 below.

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

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

Table 5: Visit Window for Parts A.1, B, C, D, and E

Visit	Target Study Day	Visit Window in Study Day
Nasopharyngeal Swabs for SARS-CoV-2		
Day 1	1 (Date of Injection)	1, Pre-first-dose
Day 29 (Month 1)	29	[2, 105]
Day 181 (Month 6)	181	[106, 274]
Day 366 (Month 12)	366	≥275
Vital Signs		
Day 1	1 (Date of First Injection)	≤1, Pre-first-dose
Day 1	1 (Date of First Injection)	1, Post-first-dose
Day 29 (Month 1)	29	[2, 105]
Day 181 (Month 6)	181	[106, 274]
Day 366 (Month 12)	366	≥275
Immunogenicity		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 15	15	[2,22]
Day 29 (Month 1)	29	[23, 105]
Day 181 (Month 6)	181	[106, 274]
Day 366 (Month 12)	366	≥275

Table 6: Visit Window for Parts A.2, F, G, H and J

Visit	Target Study Day	Visit Window in Study Day
Nasopharyngeal Swabs for SARS-CoV-2		
Day 1	1 (Date of Injection)	1, Pre-first-dose
Day 29 (Month 1)	29	[2, 60]
Day 91 (Month 3)	91	[61, 136]
Day 181 (Month 6)	181	[137, 274]
Day 366 (Month 12)*	366	≥275
Vital Signs		
Day 1	1 (Date of First Injection)	≤1, Pre-first-dose
Day 1	1 (Date of First Injection)	1, Post-first-dose
Day 29 (Month 1)	29	[2, 60]
Day 91 (Month 3)	91	[61, 136]
Day 181 (Month 6)	181	[137, 274]
Day 366 (Month 12)*	366	≥275
Immunogenicity		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 15	15	[2,22]
Day 29 (Month 1)	29	[23, 60]
Day 91 (Month 3)	91	[61, 136]
Day 181 (Month 6)	181	[137, 274]
Day 366 (Month 12)*	366	≥275

*Part A.2, Part H and Part J will not have Day 366 visit.

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

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

1. Missing or partial medication start date:

- If only Day is missing, use the first day of the month, unless:
  - The medication end date is after the date of the injection or is missing 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 the injection
- If Day and Month are both missing, use the first day of the year, unless:
  - The medication end date is after the date of the injection or is missing AND the start year of the medication coincide with the start year of the injection. In this case, use the date of the 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:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

8.4. Appendix D. Imputation Rules for Missing AE dates

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

1. Missing or partial AE start date:
   - If only Day is missing, use the first day of the month, unless:

- The AE end date is after the date of the injection or is missing 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 the injection, even if time is collected.

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

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

8.5. Appendix E. Immunogenicity Comparisons by Study Part

Endpoint	Study Part	Booster	Comparison Group*	GMT or SRR Comparison Based on Antibody Titer
Primary	A.2	50 µg mRNA-1273.214	50 µg mRNA-1273.211 (Part A.1)	within participant booster comparison against ancestral SARS-CoV-2 and SARS-CoV-2 variants (D29 and D181)
	F, Cohort 1	50 µg mRNA-1273.529	50 µg mRNA-1273 historical booster control	booster against B.1.1.529 (D29) vs. booster control against B.1.1.529 (D29)
	F, Cohort 2	50 µg mRNA-1273.529	50 µg mRNA-1273	between booster comparison against B.1.1.529 (D29)
	G	50 µg mRNA-1273.214	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against B.1.1.529 (D29 and D91)
		50 µg mRNA-1273.214	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against ancestral SARS-CoV-2 (D29 and D91)

Endpoint	Study Part	Booster	Comparison Group*	GMT or SRR Comparison Based on Antibody Titer
	H	50 µg mRNA-1273.222	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against BA.4/5 (D29)
		50 µg mRNA-1273.222	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against ancestral SARS-CoV-2 (D29)
	J	50 µg mRNA-1273.231	50 µg mRNA-1273.815	between booster comparison against SARS-CoV-2 Omicron BA.4/BA.5 (D15 and D29)
		50 µg mRNA-1273.231	50 µg mRNA-1273.815	between booster comparison against BQ.1.1 (D15 and D29)
		50 µg mRNA-1273.231	50 µg mRNA-1273.815	between booster comparison against XBB.1.5 (D15 and D29)
Secondary	A.2	50 µg mRNA-1273.214	50 µg mRNA-1273.211 (Part A.1)	within participant booster comparison against ancestral SARS-CoV-2 and SARS-CoV-2 variants (multiple time points)
	F, Cohort 1	50 µg mRNA-1273.529	50 µg mRNA-1273 historical booster control	booster vs. booster control against B.1.1.529 (D29)
		50 µg mRNA-1273.529	50 µg mRNA-1273 historical booster control	booster vs. booster control against B.1.1.529 (selected timepoints)
		50 µg mRNA-1273.529	50 µg mRNA-1273 historical booster control	booster vs. booster control against ancestral SARS-CoV-2/other variants (selected timepoints)
	F, Cohort 2	50 µg mRNA-1273.529	50 µg mRNA-1273	between booster comparison against B.1.1.529 (D29)
		50 µg mRNA-1273.529	50 µg mRNA-1273	between booster comparison against B.1.1.529 (selected timepoints)
		50 µg mRNA-1273.529	50 µg mRNA-1273	between booster comparison against ancestral SARS-CoV-2/other variants (selected timepoints)

Endpoint	Study Part	Booster	Comparison Group*	GMT or SRR Comparison Based on Antibody Titer
	G	50 µg mRNA-1273.214	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against ancestral SARS-CoV-2 (D29 and D91)
		50 µg mRNA-1273.214	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against B.1.1.529 (selected timepoints)
		50 µg mRNA-1273.214	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against ancestral SARS-CoV-2/other variants (selected timepoints)
	H	50 µg mRNA-1273.222	50 µg mRNA-1273 (Part F Cohort 2)	between booster comparison against ancestral SARS-CoV-2/other variants (selected timepoints)
Exploratory	J	50 µg mRNA-1273.231	50 µg mRNA-1273.815	between booster comparison against same strains (SARS-CoV-2 variants)

*Historical booster control arm from study mRNA-1273-P201 (50 µg mRNA-1273).

8.6. Appendix F. Summary of Major Changes in Previous Versions of SAP

Summary of major changes in SAP Version 2.0

Section	Brief Description of Changes	Rationale
2.1 (Primary Objectives), 2.2 (Secondary Objectives), 2.3 (Exploratory Objectives)	Added objectives for Part C, Part D, and Part E.	Updated to align with protocol amendment 3.
2.1 (Primary Objectives), 6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints)	Removed GMT ratio ≥1 requirement for 50 µg dose arm.	The point estimator of GMT ratio ≥1 for the 50 µg booster dose of the mRNA-1273 vaccines was considered prior to interim analyses of the 50 µg mRNA-1273 booster dose interim analyses from another

Section	Brief Description of Changes	Rationale
		mRNA-1273 clinical study (P201). These results demonstrated non-inferior immune responses, after the 50 µg booster dose, compared to the mRNA-1273 primary series and supported the emergency use authorization of the 50 µg mRNA-1273 booster dose. Therefore, the additional point estimator criterion for the 50 µg dosed is now removed from the statistical analysis plan of the P205 study.
3.1 (Primary Endpoints), 3.2 (Secondary Endpoints), 3.3 (Exploratory Endpoints)	Added endpoints for Part C, Part D, and Part E.	Updated to align with protocol amendment 3.
4.1 (Overall Study Design), 4.3 (Sample Size and Power)	Added new arm and study parts.	Updated to align with protocol amendment 3.
4.2 (Statistical Hypotheses), 6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints)	For study parts with both, 50 µg and 100 µg doses, removed testing sequence.	Results from another mRNA-1273 clinical study (P201) demonstrated non-inferior immune responses, after the 50 µg mRNA-1273 booster dose, compared to the mRNA-1273 primary series and supported the emergency use authorization of the 50 µg

Section	Brief Description of Changes	Rationale
		mRNA-1273 booster dose. Therefore, the 50 µg booster dose can be evaluated independently from the 100 µg dose, without multiplicity adjustment for hypotheses testing for these two dose arms.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints), 6.4.5 (Exploratory Analysis of Antibody-Mediated Immunogenicity Endpoints)	Added analysis for Part C, Part D, and Part E.	Updated to align with protocol amendment 3.
6.4.7 (Seroresponse)	Added seroresponse definition based on pre-dose 1 of primary series.	Added a seroresponse definition to calculate seroresponse rate based on both, pre-dose 1 of primary series and pre-booster dose antibody titers.

Summary of major changes in SAP Version 3.0

Section	Brief Description of Changes	Rationale
2.1 (Primary Objectives), 2.2 (Secondary Objectives), 2.3 (Exploratory Objectives)	Added objectives for Part F, Part G, and Part A.2.	Updated according to protocol amendment 7.
3.1 (Primary Endpoints), 3.2 (Secondary	Added endpoints for Part F, Part G, and Part A.2.	Updated according to protocol amendment 7.

Endpoints), 3.3 (Exploratory Endpoints)		
4.1 (Overall Study Design), 4.2 (Statistical Hypotheses), 4.3 (Sample Size and Power)	Added details for Part F, Part G, and Part A.2.	Updated according to protocol amendment 7.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints), 6.4.5 (Exploratory Analysis of Antibody-Mediated Immunogenicity Endpoints)	Added analysis for Part F, Part G, and Part A.2.	Updated according to protocol amendment 7.
6.4.6 (Sensitivity Analysis)	Added sensitivity analyses 1): To assess impact of positive SARS-COV-2 infection that occurs during study to antibody titer data 2): Added Multiple imputation method to impute for missing antibody titer for primary endpoint if percentage of missing value at analysis visit is more than 10%	1) Natural immunity can also increase antibody titer level, excluding SARS-CoV-2 infection up to the analysis visit to assess treatment effect without the impact of infection on immune response 2) Per FDA recent feedback (IND 19745.291)
6.4.7 Seroresponse	Clarify for Part F cohort 2, Part G, seroresponse will	

	be based on pre-vaccination baseline.	

Summary of major changes in SAP Version 4.0

Section	Brief Description of Changes	Rationale
6.1 (General consideration)	If a participant received off-study COVID-19 vaccine, the participant's immune response and effectiveness data will be censored at the earlier date of date of off-study COVID-19 vaccine, database lock/data snapshot or data cutoff date, or date of last observed in study	Once a participant receive additional off-study COVID-19 booster dose, this participant immunogenicity and infection data is no longer a pure response of on-study COVID-19 booster dose, records post additional COVID-19 booster dose need to be excluded.

Summary of major changes in SAP Version 5.0

Section	Brief Description of Changes	Rationale
2.1 (Primary Objectives), 2.2 (Secondary Objectives), 2.3 (Exploratory Objectives)	Added objectives for Part H.	Updated according to protocol amendment 9.
3.1 (Primary Endpoints), 3.2 (Secondary	Added endpoints for Part H.	Updated according to protocol amendment 9.

Endpoints), 3.3 (Exploratory Endpoints)		
4.1 (Overall Study Design), 4.2 (Statistical Hypotheses), 4.3 (Sample Size and Power)	Added details for Part H.	Updated according to protocol amendment 9.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints)	Revised the GMR non-inferiority boundary for all study parts, from ≥ 0.67 to > 0.667.	Updated according to protocol amendment 9.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints), 6.4.4 (Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints)	Added analysis for Part H.	Updated according to protocol amendment 9.
6.4.7 Seroresponse	Added evaluation of seroresponse will be based on both definitions for all study parts.	Updated according to protocol amendment 9.

Summary of major changes in SAP Version 6.0

Section	**Brief Description of Changes**	**Rationale**
2.1 (Primary Objectives), 2.3 (Exploratory Objectives)	Added objectives for Part J.	Updated according to protocol amendment 10.

3.1 (Primary Endpoints), 3.3 (Exploratory Endpoints)	Added endpoints for Part J.	Updated according to protocol amendment 10.
4.1 (Overall Study Design), 4.2 (Statistical Hypotheses), 4.3 (Sample Size and Power), 4.4 (Randomization)	Added details for Part J.	Updated according to protocol amendment 10.
6.4.3 (Primary Analysis of Antibody-Mediated Immunogenicity Endpoints)	Added details for Part J.	Updated according to protocol amendment 10.
6.5.1.1 (Derivation of SARS-CoV-2 Infection), 6.5.1.2 (Derivation of Asymptomatic SARS-CoV-2 Infection)	Added clarification on derivation. SARS-CoV-2 negative status is required when positive test result is based on serology test post baseline.	Added clarification.
6.6 Interim Analysis	Added information for Part J.	Updated according to protocol amendment 10.
6.8 Final Analysis	Added information for Part J.	Updated according to protocol amendment 10.