ModernaTX, Inc.

Protocol mRNA-1283-P301

A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ≥12 years and for the prevention of COVID-19

Investigational Medicinal Products: mRNA-1283.222, mRNA-1273.222 mRNA-1283.815, mRNA-1273.815

Statistical Analysis Plan

Amendment 3

SAP Version 4.0

Version Date of SAP: 27 February 2025

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Confidential

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTX, Inc.**
Protocol Number:	**mRNA-1283-P301**
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SAP Title:	A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ≥12 years for the prevention of COVID-19
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Document History

Version	Date	Description of main modifications	Rationale
1.0	10 Oct 2023	Original Version (Version 1.0)	
2.0	13 Feb 2024	Amendment 1 (Version 2.0)	Updated according to protocol amendment 3
		Updated primary, secondary, and exploratory objectives for two study parts: Section 2.1 (Primary Objectives) Section 2.2 (Secondary Objectives) Section 2.3 (Exploratory Objectives)	
		Updated primary, secondary, and exploratory endpoints for two study parts: Section 3.1 (Primary Endpoints) Section 3.2 (Secondary Endpoints) Section 3.3 (Exploratory Endpoints)	
		Updated for two parts: Section 4.1 (Overall Study Design) Section 4.2 (Statistical Hypotheses) Section 4.3 (Sample Size and Power)	
		Updated Analysis Set based on two Parts: Section 5 Analysis Sets	
		Updated censoring rules for primary endpoint analysis: Section 6 Analysis approach for primary rVE objective	
		Added Section 6.4.4.3 Derivation of Secondary Efficacy Endpoint: Severe COVID-19	
		Add Section 6.9 Multiplicity Adjustments	
		Removed TEAE wording: Section 6.5.1	Clarify the adverse event definition

Version	Date	Description of main modifications	Rationale
		Table 10: Primary estimand for rVE primary objective While on treatment strategy will be used for participants who take off-study COVID-19 vaccine, participants will be censored at the time of off-study COVID-19 vaccine use.	To avoid potential confounding with treatment effect of study drug.
3.0	01 July 2024	Amendment 2 (Version 3.0)	
		Added Section 9.8 Appendix H Country Specific Requirements - Japan	Align with mRNA-1283-P301 Protocol Amendment 2-JPN-2 Section 10.7
		Updated primary, secondary, and exploratory objectives for Part 3: Section 2.1 (Primary Objectives) Section 2.2 (Secondary Objectives) Section 2.3 (Exploratory Objectives) Remove Part 2: Section 2.1 (Primary Objectives) Section 2.2 (Secondary Objectives) Section 2.3 (Exploratory Objectives)	Align with mRNA-1283-P301 Protocol Amendment 3-USA-1 The study Part 2 was not implemented due to early efficacy success in Part 1. To clarify final analysis will be performed for each individual study part. Corrected a typographical error.
		Updated primary, secondary, and exploratory endpoints for Part 3: Section 3.1 (Primary Endpoints) Section 3.2 (Secondary Endpoints) Section 3.3 (Exploratory Endpoints) Remove Part 2: Section 3.1 (Primary Endpoints) Section 3.2 (Secondary Endpoints)	

Version	Date	Description of main modifications	Rationale
		Section 3.3 (Exploratory Endpoints)	
		Updated for Part 3: Section 4.1 (Overall Study Design) Section 4.3 (Sample Size and Power) Section 4.4 (Randomization) Updated to remove Part 2: Section 4.1 (Overall Study Design) Section 4.4 (Randomization)	
		Included latest version: mRNA-1283-P301 Data Blinding Plan Version 2.0: Section 4.5 (Blinding and unblinding)	
		Updated Analysis Set to include Part 3 and remove Part 2: Section 5 Analysis Sets	
		Updated Immunogenicity/Safety Analysis for Part 3: Section 6.3 (Immunogenicity Analysis) Section 6.5 (Safety Analysis) Updated treatment group to remove Part 2: Section 6.1.7 Treatment groups Updated Immunogenicity/Efficacy/Safety Analysis to remove Part 2: Section 6.3 (Immunogenicity Analysis) Section 6.4 Efficacy Analysis Section 6.5 (Safety Analysis)	

Version	Date	Description of main modifications	Rationale
		Changed 2-sided p-value to 1-sided p-value, added additional rVE information. Section 6.4.2 (Analysis Approach for Primary rVE Objective) Updated interim analysis for Part 3: Section 6.8.1 (Interim Analysis) Section 6.8.2 (Final Analysis)	
		Removed the original Figure 1 and referred to protocol Amendment 3-USA-1 Figure 1 for study schema: Section 4.1 (Overall Study Design) Updated the original Figure 2 to Figure 1, and updated ' Hypotheses Testing Strategy' to remove Part 2 in the figure: Section 4.2 Statistical Hypothesis	
4.0	27 February, 2025	Section 6.5 (Safety Analysis), Section 7 (Changes from Planned Analyses in Protocol, Section 9.8 (Appendix H Country Specific Requirements-Japan: Section 5.5-Safety Analysis) To clarify that for Part 3, COVID-19 and SARS-CoV-2 infections are not considered efficacy endpoints; therefore, confirmed and suspected COVID-19 events will be counted as unsolicited adverse events.	To align with regulatory agency's guidance.

Version	Date	Description of main modifications	Rationale
		Section 6.3.5 (Sensitivity Analysis for Part 1), Section 9.8 (Appendix H Country Specific Requirements-Japan: Section 5.3.2 Analysis for the Secondary Immunogenicity Objectives) Included a sensitivity analysis for immunogenicity endpoints at the final analysis, excluding data from participants after they have had a SARS-CoV-2 infection.	Participants immunogenicity data are likely influenced by SARS-CoV-2 infection, potentially confounding the treatment effect.
		Section 6.9 (Multiplicity Adjustment) Updated n_2 to $\tilde{n}_2$ in CHW test description	Corrected a typographical error.
		Section 6.4.7 (Analysis for Exploratory Efficacy Endpoint)	To clarify that summary of SARS-CoV-2 infection by variants may be provided for breakthrough SARS-CoV-2 infections

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Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance model
AR	adverse reaction
BA.4/5	BA.4/BA.5
bAb	binding antibody
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	Contract Research Organization
CSP	clinical study protocol
CSR	clinical study report
D	day
DBP	Data Blinding Plan
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
FDA	U.S. Food and Drug Administration
FAS	full analysis set
GCP	Good Clinical Practice
GLSM	geometric least square mean

Abbreviation	Definition
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GM	geometric mean
HCP	healthcare practitioner
HR	hazard ratio
IA	Interim Analysis
IB	investigator's brochure
IcEv	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonization
IP	investigational product
IRT	Interactive Response Technology
LLOQ	lower limit of quantification
LTFU	lost to follow-up
MAAE	medically attended adverse event
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MMRM	mixed model for repeated measures
mRNA	messenger ribonucleic acid
N	number
nAb	neutralizing antibody
NP	nasopharyngeal
PCR	polymerase chain reaction
PP	Per-Protocol
PPSE	Per-Protocol Set for Efficacy

Abbreviation	Definition
PPIS	Per-Protocol Immunogenicity Subset/Set
PT	preferred term
Q1	first quartile
Q3	third quartile
RBD	receptor-binding domain
RT-PCR	reverse transcriptase polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SoA	schedule of assessments
SOC	system organ class
S protein	spike protein
SRR	seroresponse rate
ULOQ	upper limit of quantification
UK	United Kingdom
USA	United States of America
VOC	variant of concern
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

Study mRNA-1283-P301 is a Phase 3 randomized, observer-blind, active-controlled, multicenter, 2-stage, group-sequential study.

This amended statistical analysis plan (SAP) describes the planned analyses for Study mRNA-1283-P301 and is based on the approved country specific clinical study protocol (CSP) amendments 3-USA-1 dated 16-May-2024 and amendment 2-JPN-2, dated 19-Jan-2024, and the most recent approved electronic case report form (eCRF) v13.004, dated 27-Sep-2025. The primary purpose of this SAP amendment is to clarify that confirmed and suspected COVID-19 events will be counted as unsolicited adverse events (AEs) in Part 3, as COVID-19 and SARS-CoV-2 infections are not considered efficacy endpoints in this study part.

In December 2023, protocol amendment 3 (global) was implemented to increase the total sample size to enable a pooled relative vaccine efficacy analysis and revised the rVE noninferiority comparison between mRNA-1283 and mRNA-1273 to a 10% margin. This amendment added a Part 2 to enroll up to approximately 22,074 participants to increase the total sample size based on an adaptive, 2-stage group sequential design. This adaptive study design required the study's DSMB to review interim rVE information in a closed session after a minimum number of COVID-19 events were accrued, as further described in Section 4.3. The DSMB reviewed this rVE information and provided a recommendation to the sponsor based on pre-specified rVE decision rules (see Section 4.3). Given that early efficacy was met, the DSMB recommend not enrolling Part 2. In May 2024, Part 3 was introduced in Amendment 3-USA (country specific amendment) to evaluate safety, reactogenicity and immunogenicity of mRNA-1283.815 in participants that have not previously received a COVID-19 vaccine, in adolescents, as well as generate safety, reactogenicity and immunogenicity data with commercially representative product in healthy adults.

This document also includes the analyses for mRNA-1283-P301 Protocol Amendment 2-JPN-2. The Japan Cohort was added to evaluate the safety, reactogenicity and

immunogenicity of mRNA-1283.815 compared to mRNA-1273.815 in approximately 692 Japanese participants.

Since Part 2 was not implemented due to early efficacy success in Part 1, Part 2 objectives, endpoints and analysis are removed from this SAP.

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

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

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

2. Study Objectives

The purpose of this study is to evaluate the safety, immunogenicity, and relative vaccine efficacy (rVE) of mRNA-1283 vs. mRNA-1273 (variant formulations). Study Parts 1 and 2[1] support the primary objectives, including the primary rVE objective.

Study Part 3 supports the evaluation of commercially representative investigational product in adolescents and adults, as well as unvaccinated participants. The study

[1] As noted in Section 1, due to achieving early efficacy, Part 2 of mRNA-1283-P301 was not implemented.

objectives (including Part 1, and Part 3-USA only) to be evaluated are outlined below. Part 2 was removed from this section because it is no longer applicable.
The objectives for the Japan cohort include safety, reactogenicity, and immunogenicity of mRNA-1283.815 compared to mRNA-1273.815, as outlined in Appendix H.

2.1. Primary Objectives

The primary objectives are the following:
Part 1:

- To demonstrate a non-inferior neutralizing antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against Omicron BA.4/5 based on GMR and SRR difference at Day 29.
- To demonstrate a non-inferior neutralizing antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against the ancestral SARS-CoV-2 D614G based on GMR and SRR difference at Day 29.
- To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.
- To evaluate the safety and reactogenicity of 10 µg mRNA-1283.222.

Part 3 (USA only):

- To evaluate the safety and reactogenicity of 10 µg mRNA-1283.815.

2.2. Secondary Objectives

The secondary objectives are following:
Part 1:

- To characterize the neutralizing antibody response against Omicron BA.4/5 and the ancestral SARS-CoV-2 D614G (1283.222 and 1273.222) at all timepoints.
- To assess the incidence of SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).

Part 3 (USA only):

- To evaluate the neutralizing antibody response against Omicron XBB.1.5 (mRNA-1283.815 vs mRNA-1273.815) at Day 29 in previously unvaccinated study participants.
- To characterize the neutralizing antibody response against Omicron XBB.1.5 (mRNA-1283.815 and mRNA-1273.815) at Day 29 in all study participants.

2.3. Exploratory Objectives

The exploratory objectives are the following:

Part 1:

- To characterize the antibody response against emerging variants.
- To characterize SARS-CoV-2 isolates.
- To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19.

Part 3 (USA only):

- To characterize the neutralizing antibody response against Omicron XBB.1.5 (mRNA-1283.815 and mRNA-1273.815) at all time points in all study participants.
- To characterize the antibody response against emerging variants.

3. Study Endpoints

The study endpoints (including Part 1, and Part 3-USA only) to be evaluated are outlined below.

The endpoints for the Japan cohort include safety, reactogenicity, and immunogenicity of mRNA-1283.815 compared to mRNA-1273.815, as outlined in Appendix H.

3.1. Primary Endpoints

Part 1:

The primary immunogenicity objective will be evaluated by 4 co-primary immunogenicity endpoints:

- GMR of Omicron BA.4/5 mRNA-1283.222 10 µg over the Omicron BA.4/5 mRNA-1273.222 50 µg at Day 29.
- SRR difference of Omicron BA.4/5 between mRNA-1283.222 10 µg and mRNA-1273.222 50 µg at Day 29.
- GMR of the ancestral SARS-CoV-2 D614G mRNA-1283.222 10 µg over the ancestral SARS-CoV-2 D614G mRNA-1273.222 50 µg at Day 29.
- SRR difference of ancestral SARS-CoV-2 D641G between mRNA-1283.222 10 µg and mRNA-1273.222 50 µg at Day 29.

The primary rVE objective will be evaluated by the following efficacy endpoints:

- rVE of mRNA-1283 as compared to mRNA-1273 to prevent the first event of COVID-19 starting 14 days after study injection. The rVE is defined as the percent of reduction in the hazards of the first occurrence of COVID-19 (mRNA-1283.222 vs. mRNA-1273.222) starting 14 days after study injection.

The CDC-defined COVID-19 case definition (primary definition):

  - The presence of ≥1 CDC listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); AND
  - A positive RT-PCR test

Protocol-defined COVID-19 case definition (secondary definition). The participant must have:

- Experienced ≥2 systemic symptoms: Fever (≥38°C/100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- Experienced ≥1 respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- ≥1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive RT-PCR test.

Part 1, and Part 3 (USA only):

The primary safety objective will be evaluated by the following safety endpoints for Part 1 and Part 3:

Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after the study injection.

- Unsolicited Advert Events (AEs) during the 28-day follow-up period after the study injection.
- Serious AEs (SAEs) through the entire study period.
- Medically attended AEs (MAAEs) through the entire study period.
- AEs leading to withdrawal through the entire study period.
- AE of special interest (AESI) through the entire study period.

Based on feedback received from the FDA, the following changes in the planned analysis occurred: 1) SARS-CoV-2 (symptomatic or asymptomatic) is to be an efficacy endpoint, and not counted as an AE; 2) A solicited adverse reaction should only be counted as an unsolicited AE when it meets serious criteria.

As Study mRNA-1283-P301 was ongoing, and Part 1 enrollment was completed, data collection in the eCRF was not changed. However, the changes will be performed using data mapping at the analysis stage. Below are differences between the protocol and analysis/data mapping:

RT-PCR confirmed SARS-CoV-2 infection (Protocol Section 8.3.6)

RT-PCR confirmed COVID-19 cases will not be counted as MAAEs.

Any SARS-CoV-2 infection will not be counted as AE or an SAE.

Solicited ARs during a 7-day follow-up period after the study injection (Protocol Section 8.4.6)

Solicited ARs will only be counted as an unsolicited AE when it meets serious criteria.

3.2. Secondary Endpoints

3.2.1. Immunogenicity Endpoints

Part 1:

- Omicron BA.4/5 and ancestral SARS-CoV-2 D614G GMs at all planned timepoints (Days 91, 181, 365).
- SRR against Omicron BA.4/5 and ancestral SARS-CoV-2 D614G at all planned timepoints.

Part 3 (USA only):

- Omicron XBB.1.5 GMTs at Day 29 in unvaccinated study participants.
- SRR against Omicron XBB.1.5 at Day 29 in unvaccinated study participants.
- Omicron XBB.1.5 GMTs at Day 29 in all study participants.
- SRR against Omicron XBB.1.5 at Day 29 in all study participants.

3.2.2. Efficacy Endpoints

Part 1

- SARS-CoV-2 infection (symptomatic or asymptomatic):

  Asymptomatic SARS-CoV-2 infection is defined as absence of symptoms and:

  - a positive RT-PCR test on a respiratory sample, or

- a positive serologic test for anti-nucleocapsid antibody for those participants with negative SARS-CoV-2 status at baseline.

3.3. Exploratory Endpoints

Part 1:

- GMs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints post-boost.
- Characterize the SARS-CoV-2 genomic sequence of viral isolates.
- Characterize Immune response markers

Part 3 (USA only):

- Omicron XBB.1.5 GMs at Day 91 and Day 181 in all study participants.
- SRR against Omicron XBB.1.5 at Day 91 and Day 181 in all study participants.
- GMs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.

4. Study Design

4.1. Overall Design

This is a Phase 3 randomized, observer-blind, active-controlled, multicenter, 2-stage, group-sequential study. The study planned to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1283.222 in Part 1 and of mRNA-1283.815 in Part 2 and Part 3. A group sequential design was planned for Part 1 and Part 2 to enable a pooled rVE assessment of Part 1 and Part 2. It should be noted that Part 2 was not implemented due to achieving early efficacy success in Part 1. Part 3 is an independent study part to assess reactogenicity, safety, and immunogenicity of commercially representative investigational product in adolescents, previously unvaccinated participants, and adults.

In Part 1, approximately 11,500 participants completed enrollment with mRNA-1283.222 or mRNA-1273.222. The rVE (mRNA-1283 vs mRNA-1273) from Part 1 will be assessed.

In Part 3, up to approximately 1000 adolescent participants, 600 previously unvaccinated participants, and 500 adults will be randomized 1:1 to mRNA-1283.815 or mRNA-1273.815.

The study randomization used age as a stratification factor (12 to <18, 18 to <65, and ≥65 years of age) for Part 1. Approximately 2000 (~1000 each in Part 1 and Part 3) adolescents (12 to <18 years) and approximately 30% of participants in the ≥65 years of age will be enrolled (approximately 30% for Part 1 and approximately 30% of adults for Part 3). In Part 3, previous COVID-19 vaccination status (Yes/No) will be an additional stratification factor.

The study schema is presented in protocol Amendment 3-USA-1 Figure 1.

The potential number of participants in the treatment group is described in Table 1.

Table 1 Study Arm and Dose Level in Part 1, and Part 3

Treatment Group	Vaccination Received		Total Dose	Approximate N (total)	
	Part 1	**Part 3**		Part 1	**Part 3**
1	mRNA-1283.222	mRNA-1283.815	10 µg	~5750	Up to approximately 1050
2	mRNA-1273.222	mRNA-1273.815	50 µg	~5750	Up to approximately 1050

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

Japan Cohort: Approximately 692 Japanese participants were enrolled in a randomized, observer-blinded cohort that mirrors the global study with the recommended variant of concern for the 2023/2024 respiratory season, as outlined in Appendix H.

In Part 1 of the global study, all participants were to have previously received a primary series of an authorized/approved COVID-19 vaccine and those aged ≥18 years were to have received at least 1 booster dose. Participants 12 to <18 years had no requirement to have received a booster prior to entry. In Part 3, prior vaccination is not required.

Medically stable individuals, ages 12 and above, will be screened and enrolled. Participants with chronic diseases requiring ongoing medical intervention or within the last 2 months prior to enrollment will be excluded. Participants with immunocompromising conditions or medications, or malignancy within 5 years (excluding nonmelanoma skin cancer), will also be excluded. Participants who received a COVID-19 vaccine within 90 days prior to enrollment or had positive SARS-CoV-2 testing by an authorized/approved lateral flow/rapid antigen or PCR within 90 days prior to enrollment will be excluded as well.

Study visits will consist of a Screening Visit, Vaccination Visit at Day 1, and subsequent in-person visits on Day 29 (Month 1), Day 91 (Month 3), Day 181 (Month 6), and Day 365 (Month 12), with up to 12 months of study participation in Part 1, and up to 6 months of study participation in Part 3 (up to Day 181, Month 6).

Monitoring for COVID-19 and SARS-CoV-2 infections is conducted in Part 1 to support the primary rVE objective. Part 3 will not include COVID-19 surveillance. Therefore, illness visits for potential symptoms of COVID-19 include a nasal swab for SARS-CoV-2 PCR testing in Part 1, whereas illness visits in Part 3 will not include a nasal swab for PCR testing. Illness visits in Part 3 will continue to be triggered for the evaluation of adverse reactions or adverse events as described under the schedule of assessments.

Protocol Table 1 displays the study SoA.

The study is observer-blind where only delegated unblinded study personnel responsible for study vaccine preparation, administration and/or accountability will have access to study treatment assignments. Neither the participant nor participant's parent(s)/legal guardian(s) nor the investigator nor clinical staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study. The investigator may unblind in the event of an emergency.

Participants may experience AEs that necessitate an illness visit. There may also be situations in which the investigator asks a participant to report for an illness visit following the report of an AE. Additional examinations may be conducted at these visits as necessary

to ensure the safety and well-being of participants during the study. eCRFs should be completed for each illness or unscheduled visit.

4.2. Statistical Hypothesis

There is no statistical hypothesis testing in Part 3.

4.2.1. Primary Hypothesis for the 4 co-primary Immunogenicity Endpoints (Part 1)

The primary immunogenicity analysis of booster dose vaccine response (shown by pseudotyped virus neutralizing antibody GM level) against the specific variant will be performed using the noninferiority tests of the 4 null hypotheses based on the 4 Co-primary immunogenicity endpoints, respectively.

Co-primary Endpoint 1:

The null hypothesis H^1_0: Antibody geometric mean (GM) after the mRNA-1283.222 booster dose (10 µg) against Omicron BA.4/5 is inferior to that after mRNA-1273.222 booster dose (50 µg), against Omicron BA.4/5, based on the geometric mean ratio (GMR) defined as the ratio of GM of mRNA-1283.222 at Day 29 over the GM of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).

Co-primary Endpoint 2:

The null hypothesis H^2_0: Antibody seroresponse rate (SRR) after the mRNA-1283.222 booster dose (10 µg) against Omicron BA.4/5 is inferior to that after mRNA-1273.222 booster dose (50 µg) against Omicron BA.4/5, based on the SRR difference defined as the SRR of mRNA-1283.222 against Omicron BA.4/5 at Day 29 minus the SRR of mRNA-1273.222 against the same variant at Day 29. The prespecified non-inferiority margin is 10%.

Co-primary Endpoint 3:

The null hypothesis H^3_0: Antibody GM after the mRNA-1283.222 booster dose (10 µg) against the ancestral SARS-CoV-2 D614G is inferior to that after mRNA-1273.222 booster dose (50 µg) against the ancestral SARS-CoV-2 D614G, based on the GMR defined as the

ratio of GM of mRNA-1283.222 at Day 29 over the GM of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).

Co-primary Endpoint 4:

The null hypothesis H^4_0: Antibody SRR after mRNA-1283.222 booster dose (10 µg) against the ancestral SARS-CoV-2 D614G is inferior to that after mRNA-1273.222 booster dose (50 µg) against the ancestral SARS-CoV-2 D614G, based on the SRR difference defined as the SRR of mRNA-1283.222 against the ancestral SARS-CoV-2 D614G at Day 29 minus SRR of mRNA-1273.222 against the same variant at Day 29. The prespecified non-inferiority margin is 10%.

The non-inferiority in the GMR at Day 29 after mRNA-1283.222 booster dose (10 µg) against the specific variant compared to mRNA-1273.222 booster (50 µg) against the same variant will be demonstrated if the lower bound of 2-sided 95% confidence interval (CI) of GMR >0.667.

The non-inferiority in the SRR difference at Day 29 after mRNA-1283.222 booster dose (10 µg) against the specific variant compared to mRNA-1273.222 booster (50 µg) against the same variant will be demonstrated if the SRR difference 2-sided 95% CI lower bound >-10%.

The seroresponse will be based on the following two definitions:

(1) Seroresponse at the participant level is defined as an antibody value change from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline is ≥4 × LLOQ.
(2) Seroresponse at the participant level is defined as an antibody value change from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

Definition (1) is the primary definition of SRR, and definition (2) is a secondary definition that will be used in sensitivity analyses.

The study would meet the primary immunogenicity objectives if non-inferiority is demonstrated in the 4 co-primary immunogenicity endpoints (SRR will be based on primary definition).

4.2.2. Primary Hypothesis for rVE (Part 1)

The primary endpoint on efficacy analysis of rVE will be performed using Part 1 (Part 2 was not implemented). The rVE is defined as the percent of reduction in the hazards of the first occurrence of COVID-19 (mRNA-1283 vs. mRNA-1273) starting 14 days after the study injection.

Two sets of COVID-19 case definition are defined (Section 3.1).

- CDC-defined COVID-19 case definition (primary definition):
- Protocol-defined COVID-19 case definition (secondary definition).

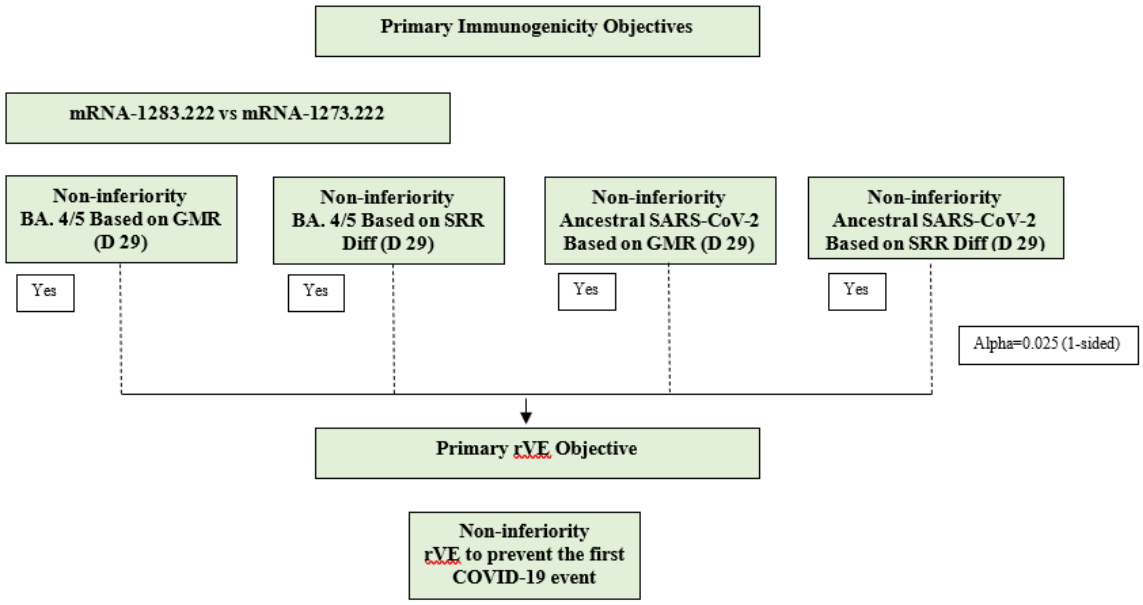
The CDC-defined COVID-19 case definition will be used as the primary COVID-19 definition and the protocol-defined COVID-19 case definition will be used as the secondary definition. The secondary definition will be used for sensitivity analysis.

The null hypothesis H_0: rVE $\leq$-10% (this is equivalent to HR $\geq$1.1, where rVE = 1-HR), which is rVE of mRNA-1283 compared to mRNA-1273 is inferior to prevent the first occurrence of COVID-19. The prespecified non-inferiority margin is 10%.

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1283 and mRNA-1273 (variant formulation) at an alpha-adjusted significance level. Section 6.9 provides details of how to assess non-inferiority under the framework of 2-stage group sequential adaptive design with sample size re-estimation.

The hypothesis for the rVE endpoint will be tested based on CDC-defined Covid-19 if all 4 co-primary immunogenicity endpoints are met (Figure_1).

Figure 1 Hypotheses Testing Strategy



Abbreviations: BA.4/5 = BA.4/BA.5; COVID-19 = coronavirus disease 2019; D = day; Diff = difference; GMR = geometric mean ratio; mRNA = messenger ribonucleic acid; rVE = relative vaccine efficacy; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

4.3. Sample Size and Power

Parts 1 and Part 2[2]:

The total number of participants to be enrolled is up to approximately 33,574 (Part 1 and 2 combined).

- Part 1: Approximately 11,500 participants were randomized to 2 groups (mRNA-1283.222 vs. mRNA-1273.222) based on a 1:1 ratio.
- Part 2[2]: Up to approximately 22,074 participants will be randomized to 2 groups (mRNA-1283.815 vs mRNA-1273.815) using a 1:1 ratio. The Part 2 sample size will be further determined after the DSMB review of the rVE interim analyses.

[2] As noted in Section 1, due to achieving early efficacy, Part 2 of mRNA-1283-P301 was not implemented.

The sample size is based on the number of COVID-19 events (first occurrence) needed for a non-inferiority rVE analysis (mRNA-1283 vs mRNA-1273). Based on proportional hazard assumption and with a 1:1 randomization ratio, a total of 2087 events/~20,122 participants (Part 1 and Part 2 total sample size) will provide approximately 80% power to demonstrate non-inferiority with a 10% margin at 1-sided alpha of 0.025.

The following assumptions are made for power calculation:

- Target rVE is 3% (mRNA-1283 vs. mRNA-1273).
- COVID-19 incidence rate is 1 per 100-person months for the first 6 months after study vaccination and 1.25 per 100-person months for Month 6 to Month 12 after study vaccination.
- 12-month dropout rate of ≃ 10% (including off-study COVID-19 vaccine use which will result in censoring COVID-19 event from the timepoint an off-study COVID-19 vaccine was used).

An interim rVE analysis based on Part 1 COVID-19 event information will be performed when at least 700 COVID-19 events have been confirmed. The O'Brien-Fleming boundary will be used for efficacy and futility (O'Brien and Fleming 1979). The purpose of this interim analysis is to assess whether the target number of COVID-19 events need to be increased to 3500 to ensure adequate power for rVE objective, and the interim decision rules will be based on observed conditional power.

The conditional power is defined as the probability of rVE success at the end of the trial (demonstration of rVE non-inferiority with a 10% margin) based on the observed rVE at the interim analyses and the originally estimated total number of COVID-19 events needed (ie, 2087 events), assuming the same data trend (Mehta and Pocock 2011). The DSMB will make a recommendation to the Sponsor based on the following prespecified rules:

1. If the observed rVE meets success criteria for efficacy based on the O'Brien-Fleming boundary, the DSMB will inform the Sponsor regarding early success (rVE objective) due to overwhelming efficacy. If the early success criterion is not met, then:

2. If the conditional power ≥0.8, the DSMB will recommend that the Sponsor may initiate Part 2 enrollment to accrue approximately 2087 COVID-19 events (Part 1 and Part 2 combined); it is estimated that approximately 8622 participants should be enrolled in Part 2 for a total of approximately 20,122 participants (Part 1 and Part 2 combined).
3. If the conditional power is ≥0.35 and <0.8, the DSMB will recommend that the Sponsor may initiate Part 2 enrollment to accrue approximately 3500 COVID-19 events (Part 1 and Part 2 combined); it is estimated that approximately 22,074 participants need to be enrolled for a total of approximately 33,574 participants (Part 1 and Part 2 combined). The number of 3500 COVID-19 events is needed when the target rVE is assumed to be zero, instead of 3%.
4. If the conditional power <0.35, the DSMB will inform the Sponsor that further enrollment might not lead to a favourable outcome.
5. If the interim rVE crosses the O'Brien-Fleming futility boundary, the DSMB will recommend not enrolling Part 2.

Under any of the above circumstances, the sponsor will ultimately be responsible for the decision about further enrollment (Part 2). Given that the rVE objective was met based on Part 1 COVID-19 events accrued through January 31, 2024, there was no Part 2 enrollment.

An example of observed rVEs and corresponding conditional power was provided in Appendix G Table 11 (assuming interim rVE occurred at time when study accrued ~1000 COVID-19).

Sample size of the immunogenicity subset to support the primary immunogenicity objective: a subset of study participants from Part 1 will be used for the primary immunogenicity objective. The PP immunogenicity subset for the primary immunogenicity analysis will include participants regardless of baseline SARS-CoV-2 infection status (negative or positive). With approximately 882 evaluable participants (441:441 for mRNA-1283.222 vs. mRNA-1273.222) in the PP immunogenicity subset, there is approximately 90% power to demonstrate non-inferior antibody responses of mRNA-1283.222 vs. mRNA-1273.222 for each co-primary immunogenicity endpoint at 2-sided alpha of 0.05. The assumptions are: the true GMR against ancestral SARS-CoV-2 and BA.4/5 at Day 29 (mRNA-1283.222 vs. mRNA-1273.222) is 1 and the standard deviation of the natural log-transformed level is

1.8, non-inferiority margin for GMR is 1.5 (or 1/1.5 = 0.667); the true SRR against the ancestral SARS-CoV-2 D614G and against the Omicron BA.4/5 variant is 70% (same assumption for mRNA-1283.222 and mRNA-1273.222) and the non-inferiority margin for SRR difference is 10%. It is also expected that ~10% participants might be excluded from the PP immunogenicity subset (eg, reasons such as missing immunogenicity samples), and hence an immunogenicity subset sample size of 980 (490:490) is needed.

Part 3:

The sample size of Part 3 is not based on statistical hypothesis testing for immunogenicity. Participants in each group will be randomized 1:1 into mRNA-1283.815 or mRNA-1273.815.

- Up to approximately 1000 adolescents
- Up to approximately 600 unvaccinated participants
- Up to approximately 500 adults

With this sample size, there is at least a 90% probability to observe at least one participant reporting an AE if the true rate of AEs is 1.0%, with at least 1050 participants receiving the mRNA-1283 variant formulation.

4.4. Randomization

In Part 1, approximately 11,500 participants completed enrollment with mRNA-1283.222 or mRNA-1273.222. Part 2 enrollment was expected to be up to approximately 22,074 participants randomized to mRNA-1283.815 or mRNA-1273.815; however, Part 2 was not enrolled due to early efficacy success from the Part 1 rVE interim analysis (IA2). In Part 3, up to approximately 1000 adolescent participants, 600 previously unvaccinated participants, and 500 adults will be randomized 1:1 to mRNA-1283.815 or mRNA-1273.815.

The study randomization will have age as a stratification factor (12 to <18, 18 to<65, and ≥65 years of age) for Part 1. Approximately 2000 (~1000 each in Part 1 and Part 3)

adolescents (12 to <18 years) and approximately 30% of participants ≥65 years of age will be enrolled (approximately 30% for Part 1and approximately 30% of adults for Part 3). In Part 3, previous COVID-19 vaccination status (Yes/No) will be additional stratification factor.

4.5. Blinding and Unblinding

This study is observer-blind; blinding during the study will be conducted as described in protocol Section 6.4. The study participants, investigators, site personnel, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the unblinding occurs (protocol Section 6.4) or until study database is locked and unblinded.

An independent unblinded statistical and programming team who are not involved in study design and conduct of the CRO will perform the planned interim analysis. A prespecified sponsor team including biostatistician(s) and statistical programmer(s) were unblinded to treatment-group level information but remain blinded to the subject-level treatment assignment information at the Part 1 (Day 29) immunogenicity and safety interim analysis results (IA1).

The Part 1 interim rVE analysis (IA2) was reviewed by the DSMB in a closed session and the Sponsor remained blinded to any interim rVE results. Upon review of interim data, the DSMB made a recommendation to the Sponsor regarding enrollment of Part 2 based on prespecified rules (Section 4.3). The DSMB otherwise periodically reviews unblinded safety data in closed sessions.

The details regarding roles and corresponding unblinding for the study conduct were included in the mRNA-1283-P301 Data Blinding Plan Version 2.0 dated 23 Feb 2024.

Procedures for breaking the blind in the case of a medical necessity are provided in protocol Section 6.4.

5. Analysis Sets

The following analysis sets are defined for Part 1, and Part 3 (USA only), as applicable: Randomization Set, Full Analysis Set (FAS), Per-Protocol Immunogenicity Subset (PPIS), Solicited Safety Set, Safety Set and Per-Protocol Set for Efficacy (PPSE).

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized participants who receive the IP. Participants will be analyzed according to their randomized study arm.

5.3. Immunogenicity Subset

Part 1:

A subset of participants whose serum samples will be assessed in PPD bioA lab and their antibody data will be used to support the immunogenicity objectives of study mRNA-1283-P301, details of sampling method can be found in mRNA-1283-P301 Immunogenicity Data Sample Plan Version 3 dated 21 Aug 2023.

5.4. Per-Protocol Immunogenicity Subset

Part 1:

The primary analysis population to characterize immunogenicity is the Per-Protocol Immunogenicity Subset (PPIS). PPIS consists of a randomly sampled subset of trial participants who receive the planned dose of study vaccination, have baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data, and have

no major protocol deviations that impact key or critical data. Participants will be analyzed according to their randomized study treatment.

Part 3:

PPIS consists of all study participants who receive the planned dose of study vaccination, have baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data, and have no major protocol deviations that impact key or critical data. Participants will be analyzed according to their randomized study treatment. Immunogenicity analysis will be analyzed for PPIS - All Study Participants and PPIS - All Unvaccinated Study Participants, separately.

5.5. Solicited Safety Set

Part 1 and Part 3:

The Solicited Safety Set consists of all randomized 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 that they actually received.

5.6. Safety Set

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

5.7. Per-Protocol Set for Efficacy

Part 1:

The Per-Protocol Set for Efficacy (PPSE) consists of all participants in the FAS who receive the planned dose of IP and have no major protocol deviations that impact vaccine efficacy data. Participants will be analyzed according to their randomized study arm.

PPSE is not applicable for Part 3.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments (SoA) is provided in the protocol Table 1.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

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

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that vaccination group within the analysis set of interest, unless otherwise specified.

6.1.1. Baseline Value

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the injection.

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

6.1.2. Baseline SARS-CoV-2 status

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

Positive SARS-CoV-2 status at Baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Negative status is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1.

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

6.1.3. Study Day

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

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.

6.1.4. Analysis Visits and Window

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

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline measurements.
- In the derivation of maximum/minimum values after the injection 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.

6.1.5. Incomplete/missing data

- Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations and procedures, and off-study Covid Vaccine are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

6.1.6. Calculation Regarding Antibody Levels

The antibody values are reported as below the LLOQ (e.g. < 0.1), the numeric values will be substituted by 0.5 × LLOQ in the summary when treating the results as continuous variables. If the antibody values are reported as greater than the ULOQ (e.g. > 3000), the numeric values will be substituted by ULOQ in the summary statistics for continuous variable if the actual value is not available.

6.1.6.1. Calculation Regarding Geometric Mean and Geometric Mean Fold Rise (GMFR)

- The geometric mean 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 levels.

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

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

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

6.1.7. Treatment groups

The following treatment groups will be used for summary purposes based on treatment groups in each corresponding Part:

- mRNA-1283.222 10 µg
- mRNA-1273.222 50 µg
- mRNA-1283.815 10 µg
- mRNA-1273.815 50 µg

All analyses and data summaries/displays will be provided by the treatment group using appropriate analysis population unless otherwise specified.

6.1.8. Analysis Periods

For immunogenicity, safety, and efficacy analysis: data will be censored after off-study COVID-19 vaccine use. These rules will be applied across all analysis unless otherwise specified. For efficacy analysis: COVID-19 cases will also be counted after off-study COVID-19 vaccine use as sensitivity analysis. For safety analysis: Analyses may also be performed to summarize safety regardless of off-study COVID-19 vaccine use. subgroup analyses may be performed to assess safety after off-study COVID-19 vaccine use.

The following analysis periods will be used in this study:

- Up to 7 days after vaccination: include the day of injection and 6 subsequent days. This analysis period will be used for safety analyses of solicited AR, unless specified otherwise.
- Up to 28 days after vaccination: include the day of injection and 27 subsequent days: this analysis period will be used for safety analyses of Unsolicited AEs, unless specified otherwise. Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- Overall period: The efficacy analysis period starts at the injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, off-study vaccine use, data cutoff date, or death) or starts at the injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, data cutoff date, or death) for sensitivity analysis. For the safety analysis period starts at the injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, data cutoff date, date of off-study COVID-19 vaccine use, or death). The safety analyses include unsolicited AEs, MAAE, AESI, SAE and AEs leading to discontinuation from study, unless specified otherwise.

6.1.9. Subgroup

Safety, efficacy and immunogenicity endpoints may be analyzed in selected subgroups if applicable, including but not limited to, the following subgroups:

- Sex (Female, Male)
- Age (≥12 to <18 Years, ≥18 to <65 Years, ≥65 Years)
- Race (White, Black, Other etc.)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline SARS-CoV-2 Status (Positive, Negative)
- Number of prior COVID-19 booster doses (0, 1, 2, ≥3)
- Number of prior COVID-19 vaccine doses
- Country (United States, Canada, United Kingdom)

- Geographic region (North America including United States and Canada vs Europe including United Kingdom)
- Type of last prior COVID-19 vaccines (mRNA original monovalent, mRNA Omicron bivalent, non-mRNA vaccine, non-mRNA vaccine)
- Dosing interval group (Date of current dose – date of last prior dose of COVID-19 vaccine +1) (months): (e.g. ≥/< median, or by quartiles)
- Previous COVID-19 vaccination status (Yes/No)

All analyses and data summaries/displays will be provided by the treatment group using appropriate analysis population unless otherwise specified.
All analyses will be conducted using SAS Version 9.4 or higher unless otherwise specified.

6.2. Background Characteristics

6.2.1. Subject Disposition

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

- Randomization Set
- Full Analysis Set (FAS)
- Immunogenicity Subset
- Per-Protocol Immunogenicity Subset (PPIS)
- Solicited Safety Set
- Safety Set
- Per-Protocol Set for Efficacy (PPSE)

The number of participants in the following categories will be summarized based on participants screened:

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

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

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

- Received the dose of IP
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
    - Adverse Event
    - Death
    - Lack of Efficacy
    - Lost to follow-up (LTFU)
    - Non-Compliance with study drug
    - Physician decision
    - Pregnancy
    - Protocol violation
    - SAR/Reactogenicity event
    - Study terminated by sponsor
    - Withdrawal of consent by participant
    - Other

The number and percentage of randomized participants will be summarized by site based on the Randomization Set.

A subject disposition listing will be provided, including informed consent, participants who were vaccinated, participants who completed study, participants who discontinued from participation in the study, with reasons for discontinuation, site and analysis sets information, A separate listing will be provided for screen failure participants with reasons for screen failure.

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

6.2.2. Demographics and Baseline Characteristics

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

The number and percentage of participants will be provided for below baseline characteristics:

- SARS-CoV-2 status at baseline (Positive, Negative)
- Number of prior COVID-19 booster doses (0, 1, 2, ≥3)
- Number of prior COVID-19 vaccine doses
- Geographic region (North America including United States and Canada vs Europe including United Kingdom)
- Dosing interval group (Date of current dose – date of last prior dose of Covid-19 vaccine +1) (months): (e.g. ≥/< median, or by quartiles)
- type of last prior vaccine: mRNA original monovalent, mRNA Omicron bivalent, non-mRNA vaccine
- Previous COVID-19 vaccination status (Yes/No)

The summaries will be provided separately based on the FAS, Safety Set, PPIS and PPSE.

6.2.3. Medical History

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

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

will be displayed in descending order of frequency of mRNA-1283 and then alphabetically within SOC.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications, non-study vaccinations, and Off-study vaccine will be coded using the WHO drug dictionary (WHODD). The summary of concomitant medications will be summarized based on categorization of prior, concomitant, and post medications summarized in Appendix C Table 8 for Safety set.

The number and percentage of participants who continued or newly received concomitant medications and non-study vaccinations will be summarized by treatment group by PT in descending frequency in the mRNA-1283 group:

- Any concomitant medications
- Any non-study vaccine
- Off-study COVID-19 vaccine
- Antipyretics or analgesics medication, summaries will be provided for during the 7-day follow-up period of the injection.

Prior, concomitant and post medications, Off-study covid vaccine will be presented in a listing.

Concomitant Procedures may be presented in a listing.

6.2.5. Study Exposure

Study IP administration data will be summarized in a disposition table and presented in a listing.

A Dosing error listing will also be provided.

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 are developed based on the protocol and ongoing data and will be finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by vaccination group as defined in Section 6.1.7 based on the Randomization Set.

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

Major protocol deviations will be presented in a listing.

6.3. Immunogenicity Analysis

Immunogenicity data for the primary (Section 2.1), secondary (Section 2.2) and exploratory (Section 2.3) immunogenicity objective will be analyzed in this study. The PPIS will be used for the immunogenicity objectives.

6.3.1. Sampling of the Immunogenicity Subset in Part 1

For the primary analysis of immunogenicity and characterizing vaccine antibody response, a proportional stratified random sampling method was used to select a sample of trial participants to assess antibody response.

A separate document, the Sampling Plan (mRNA-1283-P301 Immunogenicity Data Sampling Plan version 3, 21 Aug 2023), provides details on the sampling process.

6.3.2. Immunogenicity Assessments

The following immunogenicity response will be assessed for Part 1 and Part 3:

Part 1 (immunogenicity subset), and Part 3:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus neutralization assays.
- Part 1 only: Serum bAb level against SARS-CoV-2 as measured by ligand binding assay specific to the SARS-CoV-2 S protein and the S protein RBD.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

6.3.3. Analysis for Primary Immunogenicity Endpoints in Part 1

The PPIS is the primary analysis population used in the immunogenicity analyses, unless otherwise specified. Participants will be included in the treatment group to which they were randomized.

The primary objective is to demonstrate a non-inferior antibody response (shown by pseudotyped virus neutralizing antibody GM level) of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against Omicron BA.4/5 and against ancestral SARS-CoV-2 at Day 29 with the study injection administered. The study would be considered as meeting the primary immunogenicity objectives if non-inferiority is demonstrated based on the 4 co-primary immunogenicity endpoints. If a participant takes off-study COVID-19 vaccine, participant immunogenicity data will be censored after the participant takes an off-study COVID-19 vaccine.

Co-primary Endpoint 1:

- GMR against Omicron BA.4/5 defined as the ratio of GM of mRNA-1283.222 at Day 29 over the GM of mRNA-1273.222 at Day 29

Co-primary Endpoint 2:

- SRR difference against Omicron BA.4/5 defined as the SRR of mRNA-1283.222 against Omicron BA.4/5 at Day 29 minus the SRR of mRNA-1273.222 against the same variant at Day 29

Co-primary Endpoint 3:

- GMR against ancestral SARS-CoV-2 D614G defined as the ratio of GM of mRNA-1283.222 at Day 29 over the GM of mRNA-1273.222 at Day 29

Co-primary Endpoint 4:

- SRR difference against ancestral SARS-CoV-2 D614G defined as the SRR of mRNA-1283.222 against Omicron BA.4/5 at Day 29 minus the SRR of mRNA-1273.222 against the same variant at Day 29

Co-primary endpoint 1 and 3 Analysis:

The immune response as measured by the serum nAb antibody GM (definition in Section 6.1.6) at Day 29 of mRNA-1283.222 group will be compared to that of mRNA-1273.222 group.

An analysis of covariance model (ANCOVA) will be carried out with the dependent variable of the serum Ab level at Day 29 and a group variable (mRNA-1283.222 vs. mRNA-1273.222) as the fixed effect, adjusted by SARS-CoV-2 status at baseline, and age group per randomization. The number of prior boosters, and type of last prior vaccine may be included in the model if applicable. The GM will be estimated by the geometric least square mean (GLSM) from the model.

The serum antibody GMR at Day 29 (mRNA-1283.222 vs. mRNA-1273.222) will be estimated by the ratio of GLSM. The GMR and its 2-sided 95% CI will also be provided to assess the difference in antibody response between mRNA-1283.222 and mRNA-1273.222.

The decision rules for the hypothesis testing of the serum Ab GMR, ie, non-inferiority criteria, will be implemented. If the lower bound of the 95% CI of the GMR is >0.667, non-inferiority of serum antibody GM of mRNA-1283.222 compared to mRNA-1273.222 will be considered demonstrated based on GMR.

Co-primary endpoint 2 and 4 Analysis:

Primary definition: Seroresponse at the participant level is defined as an nAb antibody value change from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline is ≥4 × LLOQ, where baseline refers to pre-booster.

The number and percentage of participants with seroresponse at Day 29 will be provided with 2-sided 95% CI using Clopper-Pearson method. The SRR differences with their 95% CI (using Miettinen-Nurminen score method) between the 2 groups at Day 29 will be tabulated. The non-inferiority of SRR difference of mRNA-1283.222 compared to mRNA-1273.222 will be achieved if the lower bound of the 95% CI of the SRR difference is >-10%.

6.3.4. Analysis for the Secondary or Exploratory Endpoints on Immunogenicity

SARS-CoV-2-specific nAb are assessed at multiple timepoints in each part of this study. Immunogenicity at timepoints beyond Day 29 is the secondary objective in Part 1, and Day 29 immunogenicity is a secondary objective in Part 3 (timepoints beyond Day 29 are exploratory). Also, SARS-CoV-2-specific bAb are assessed as an exploratory endpoint in Part 1.

6.3.4.1.GM, GMFR and GMR of nAb and bAb Level Against SARS-CoV-2-Specific Variant Analysis

Part 1:

Data from quantitative SARS-CoV-2-specific nAb and bAb value will be analyzed as below and summarized by treatment group, at each timepoint that an assessment is performed.

- GM of nAb levels against Omicron BA.4/5 with corresponding 95% CI at each planned time point.
- GM of bAb levels against Omicron BA.4/5 with corresponding 95% CI at each planned time point.

- GM of nAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each planned time point.
- GM of bAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each planned time point.
- GM of bAb levels against other SARS-CoV-2 variants with corresponding 95% CI at each planned time point.
- GMFR of postbaseline/baseline nAb levels against Omicron BA.4/5 with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.
- GMFR of postbaseline/baseline bAb levels against Omicron BA.4/5 with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.
- GMFR of postbaseline/baseline nAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.
- GMFR of postbaseline/baseline bAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.
- GMFR of postbaseline/baseline bAb levels against other SARS-CoV-2 variants with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.

The 95% CIs will be calculated based on the t-distribution of the log-transformed values for GM, and the difference of log-transformed values for GMFR, then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point: the number of participants (n), median, Q1, Q3, minimum (min) and maximum (max).

The proportion of participants with geometric mean fold-rise ≥ 2, and fold-rise ≥ 4 of serum SARS-CoV-2 specific nAb/bAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs.

In addition, GM of SARS-CoV-2-specific nAb/bAb levels with corresponding 95% CI will be plotted at each timepoint.

The mixed model for repeated measures (MMRM) will be used to analyze all post-baseline antibody levels (nAb, bAb) for between treatment comparisons using SAS PROC MIXED. The model will include all available log-transformed antibody levels at each post-baseline visit as the dependent variable, treatment groups, analysis visit (as a class variable), and treatment-by-visit interaction visit as fixed effects, adjusted by SARS-CoV-2 status at baseline, age group per randomization, number of prior boosters, and type of last prior vaccine if applicable. An unstructured covariance structure will be used to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence issue due to the unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. No imputation of missing data will be done.

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

In addition, GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference between mRNA-1283 vs. mRNA-1273 group at each visit:

- GMR (mRNA-1283.222 against mRNA-1273.222) of nAb levels against Omicron BA.4/5 with corresponding 95% CI at each time point.
- GMR (mRNA-1283.222 against mRNA-1273.222) of bAb levels against Omicron BA.4/5 with corresponding 95% CI at each time point.
- GMR (mRNA-1283.222 against mRNA-1273.222) of nAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each time point.
- GMR (mRNA-1283.222 against mRNA-1273.222) of bAb levels against SARS-CoV-2 D614G with corresponding 95% CI at each time point.

- GMR (mRNA-1283.222 against mRNA-1273.222) of bAb levels against other SARS-CoV-2 variants with corresponding 95% CI at each time point.

Part 3:

Day 29 SARS-CoV-2-specific nAb value will be analyzed and summarized by treatment group for PPIS - All Study Participants, and PPIS - All Unvaccinated Study Participants, separately as below, other timepoints may also be analyzed when nAb data is available:

- GM of nAb levels against Omicron XBB.1.5 with corresponding 95% CI at Day 29.
- GMFR of postbaseline/baseline nAb levels against Omicron XBB.1.5 with corresponding 95% CI at post-baseline timepoint (Day 29) over pre-injection baseline at Day 1.

In addition, GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference between mRNA-1283 vs. mRNA-1273 group using an analysis of covariance model with the dependent variable of the serum nAb level at Day 29 and a group variable (mRNA-1283.815 vs. mRNA-1273.815) as the fixed effect, adjusted by age group per randomization and previous COVID-19 vaccination status (Yes/No), other factors may be included in the model if applicable.

6.3.4.2. Seroresponse Analysis

Part 1:

The number and percentage of participants with seroresponse (primary and secondary definition Section 4.2.1) at all planned timepoints will be provided with 2-sided 95% CI using Clopper-Pearson method, based on nAb value against Omicron BA.4/5, bAb value against Omicron BA.4/5, nAb value against SARS-CoV-2 D614G, bAb value against SARS-CoV-2 D614G, and bAb value against other SARS-CoV-2 variants separately.

The SRR differences at each visit with their 95% CI (using Miettinen-Nurminen score method) between the 2 treatment groups at each visit will be tabulated.

Part 3:

Seroresponse analysis will be analyzed for PPIS - All Study Participants and PPIS - All Unvaccinated Study Participants, separately as below:

The number and percentage of participants with seroresponse (primary and secondary definition Section 4.2.1) at Day 29 after study injection will be provided by treatment group with 2-sided 95% CI using Clopper-Pearson method.
The SRR differences at each visit with their 95% CI (using Miettinen-Nurminen score method) between the 2 treatment groups at Day 29 will be tabulated.
Seroresponse analysis may also be performed at other timepoints when nAb data is available.

6.3.5. Sensitivity Analysis for Part 1

Following Sensitivity analysis for primary immunogenicity endpoints will be performed with the same methods described in Section 6.3.3:

- In primary immunogenicity endpoints in Part 1, secondary seroresponse definition (Section 4.2.1) will be used to analyze Co-primary endpoints 2 and 4 based on PPIS with the same method described in Section 6.3.3.
- At the final analysis, a sensitivity analysis will be performed for the immunogenicity endpoints by excluding immunogenicity data from participants after they have had a SARS-CoV-2 infection.

6.3.6 Immunogenicity Subgroup Analysis

To assess consistency of antibody response across various subgroups, antibody response data will be summarized for selected subgroups when applicable. Subgroup analysis (e.g. baseline SARS-CoV-2 status, see Section 6.1.9 for a full list) for the primary immunogenicity endpoints in Part 1 may be performed using the same methods described in Section 6.3.3.

For Part 3, subgroup analyses for immunogenicity endpoints will be performed for age groups and prior COVID-19 vaccination status; other subgroup analyses may be performed if appropriate.

Analyses using a combination of subgroups may be performed when applicable. Subgroups may be combined together to have a sufficient number of participants in each subgroup. Forest plots will be provided for GMR and SRR difference, along with 95% CIs for each subgroup.

6.4. Efficacy Analysis for Part 1

Efficacy analyses will be performed using the FAS and PPSE. The primary analysis will be based on the PPSE. Efficacy analyses will be based on Part 1. Participants will be included in the treatment group to which they were randomized (mRNA-1283 [variant formulation] 10 µg vs mRNA-1273 [variant formulation] 50 µg).

6.4.1. COVID-19 Definition/Derivation for Efficacy Endpoint

The primary rVE objective is to demonstrate the non-inferior rVE of mRNA-1283 as compared to mRNA-1273 to prevent the first event of COVID-19 starting 14 days after study vaccine injection. COVID-19 is defined as symptomatic disease based on the criteria specified in Section 3 of the protocol. Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and positive RT-PCR test results.
For the duration of the study, after day 1, a nasal swab sample will be collected if signs and symptoms are suggestive of COVID-19. If participants experience symptoms suggestive of COVID-19, then participants will be directed as soon as possible and within 72 hours to obtain a SARS-CoV-2 RT-PCR test at the study site.

Two sets of COVID-19 definition will be used (Section 3.1):

- CDC-defined COVID-19 case definition (Primary definition): Presence of one of CDC listed symptoms and a positive RT-PCR test.

- Protocol-defined COVID-19 case definition (Secondary definition): Based on eligible COVID-19 symptoms (at least 2 systemic symptoms or 1 respiratory symptom) and positive RT-PCR.

6.4.1.1.Derivation of CDC-Defined COVID-19 Case Definition (Primary Definition)

CDC-defined Covid-19 will be the primary definition used for rVE analysis: the incidence of the first occurrence of COVID-19 cases meeting the CDC case definition, starting 14 days after injection.

Table 2 Derivation for COVID-19 (CDC-Defined)

	CDC- Defined Criteria for Primary Analysis
Post-baseline results	RT-PCR 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 or runny nose, nausea, vomiting, or diarrhea.

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

- Date of the positive RT-PCR test
- Date of eligible symptom for primary definition of COVID-19, defined as the earliest date of first eligible symptom is reported

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

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

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

The first occurrence of COVID-19 starting 14 days after the injection will be considered as event.

6.4.1.2. Derivation of Protocol-Defined COVID-19 Case Definition (Secondary Definition)

COVID-19 case based on protocol-defined criteria will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms, i.e. a positive RT-PCR result of the eligible symptoms summarized below in Table 3. Protocol-defined Covid-19 as secondary definition will be used as sensitivity analysis for rVE endpoint:

Table 3 Derivation for COVID-19 (Protocol-Defined)

	Protocol-Defined Criteria for Secondary Analysis
Post-baseline results	RT-PCR 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 or difficulty breathing, OR clinical or radiographical evidence of pneumonia;

The date of COVID-19 (case) will be the later date of ([2 eligible systemic symptoms reported, or 1 eligible respiratory symptom reported] and, [date of positive RT-PCR test]). Specifically, the date of COVID-19 will be the later date of the following two dates (date of positive RT-PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

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

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

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

COVID-19 cases will be counted starting 14 days after the injection, i.e. date of COVID-19 – Date of the injection ≥ 14 (starting 14 days after the injection).

6.4.2. Analysis Approach for Primary rVE Objective

The primary efficacy objective is the rVE of mRNA-1283 as compared to mRNA-1273 to prevent the first event of COVID-19 starting 14 days after study vaccine injection (censored for off-study COVID-19 vaccine use post study vaccine injection).
The analysis for primary efficacy endpoint will be performed based on CDC-defined COVID-19 case definition (primary definition).
The number and percentage of participants who had an event (i.e. the first occurrence of COVID-19 starting 14 days after the injection, date of COVID-19 – date of the injection ≥ 14) and participants who were censored will be summarized. The censoring rules of cases are outlined in Table 4 below.
The non-parametric Kaplan-Meier method will be used to estimate the time to first occurrence of COVID-19 curve in each treatment group.

Relative Vaccine efficacy (rVE) is defined as the percent reduction in the hazard of the primary efficacy endpoint (mRNA-1283 vs. mRNA-1273), i.e. one minus the hazard ratio (HR). The null hypothesis is:

$$H_0^{efficacy}: \text{relative vaccine efficacy} \leq -10\%$$

Equivalently, the null hypothesis is:

$$H_0^{efficacy}: \text{hazard ratio (HR)} \geq 1.1$$

A stratified Cox proportional hazard model including study vaccination group as a fixed effect will be used to estimate the HR (mRNA-1283 vs. mRNA-1273[variant formulation], stratified by stratification factor age group at randomization: (≥12 to <18 years, ≥18 to <65 years, or ≥65 years). Efron's method will be used to handle ties.

The HR with corresponding alpha-adjusted confidence interval (CI), 95% CI, 1-sided *p*-value for testing the null hypothesis from the stratified Cox model will be reported. Additionally, the rVE and its corresponding alpha-adjusted CI and 95% (CI) will be provided.

Table 4 Censoring Rules for COVID-19

Scenario	**Primary analysis approach for primary efficacy endpoint (cases starting ≥14 days after injection) censored for off-study COVID-19 vaccine use**	**Sensitivity Analyses**	
		Cases starting after study injection censored for off-study COVID-19 vaccine use	**Cases starting ≥14 days after injection) regardless of off-study COVID-19 vaccine use**
Early case (occurring prior to 14 days after study injection)	**Censored** at date of case or off-study COVID-19 vaccine use, whichever is earlier	**Event:** early case occurred before off-study COVID-19 vaccine use or no off-study COVID-19 vaccine use. **Censored:** at date of off-study COVID-19 Vaccine taken if early case occurred after off-study COVID-19 vaccine use	**Censored** at date of case
COVID-19 ≥14 days after injection (including participants who take off-study COVID-19 vaccine)	**Event:** COVID-19 occurred before off-study COVID-19 vaccine use or no off-study COVID-19 vaccine use. **Censored:** at date of off-study COVID-19 Vaccine taken if COVID-19 occurred after off-study COVID-19 vaccine use	**Event:** COVID-19 occurred before off-study COVID-19 vaccine use or no off-study COVID-19 vaccine use. **Censored:** at date of off-study COVID-19 Vaccine taken if COVID-19 occurred after off-study COVID-19 vaccine use	**Event**

Scenario	Primary analysis approach for primary efficacy endpoint (cases starting ≥14 days after injection) censored for off-study COVID-19 vaccine use	Sensitivity Analyses	
		Cases starting after study injection censored for off-study COVID-19 vaccine use	Cases starting ≥14 days after injection) regardless of off-study COVID-19 vaccine use
Early discontinuation or death without occurrence of COVID-19	**Censored** at data cutoff date, study discontinuation date, date of off-study COVID-19 Vaccine use, death date whichever is earlier		**Censored** at data cutoff date, study discontinuation date, death date whichever is earlier
No COVID-19 occurring after 14 days after booster			

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

6.4.3. Supportive Analysis Using Exact Method Based on Incidence Rate

As a supportive analysis, rVE will be estimated by one minus the ratio of incidence rates (mRNA-1283 vs mRNA-1273) multiplied by 100%:

rVE = 100 × (1 – ratio of incidence rates adjusting for person-time) %

Person-time is calculated as the total time (months) from date of study vaccination to the date of the first occurrence of COVID-19 in participants with COVID-19, or to the date of censoring for participants who are censored.

The incidence rate for each vaccination group will be calculated as the number of participants with an event (ie, first COVID-19 event at least 14 days post injection and up to the data cutoff for the rVE analysis) divided by the total person-time (months) in each vaccination group.

Summaries of person-time and incidence rate, and 95% CI for incidence rate, will be performed by treatment group. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.
The 95% CI of rVE will be computed using the exact method conditional upon the total number of cases adjusted by the total person-time.
The analysis will be provided based on CDC defined COVID-19 and Protocol defined COVID-19 separately.

6.4.4. Secondary Endpoints Definition/Derivation for Efficacy

6.4.4.1. Derivation of SARS-CoV-2 Infection (Symptomatic or Asymptomatic)

SARS-CoV-2 infection is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection, the incidence of SARS-CoV-2 infection counted starting 14 days after the injection (i.e. date of infection – Date of the injection ≥ 14). SARS-CoV-2 infection will be defined as follows:

- Negative bAb level against SARS-CoV-2 nucleocapsid protein (as measured by *Roche Elecsys*) and negative RT-PCR at baseline that becomes positive bAb level against SARS-CoV-2 nucleocapsid protein (as measured by *Roche Elecsys*) post-baseline, OR
- Positive RT-PCR post-baseline (at scheduled or unscheduled/illness visits).

Derivation of SARS-CoV-2 infection definition is summarized in Table 5 below.

Table 5 Derivation for SARS-CoV-2 Infection

Baseline SARS-CoV-2 Status	**Post-baseline assessments**		**Endpoint**: SARS-CoV-2 infection
	RT-PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	
	Positive (either at scheduled NP swab test, or at exposure or symptom-prompt NP swab test)		Case

Negative at Baseline (both RT-PCR test and serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid)		**Positive** (at scheduled post-baseline visits) as measured by *Roche Elecsys*	Case

The date of 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

6.4.4.2. Derivation of Asymptomatic SARS-CoV-2 Infection

The incidence of asymptomatic SARS-CoV-2 infection is measured by RT-PCR and/or serology tests obtained at post-baseline visits counted starting 14 days after 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:
    - Negative bAb level against SARS-CoV-2 nucleocapsid protein (as measured by Roche Elecsys) and Negative RT-PCR at baseline that becomes positive bAb level against SARS-CoV-2 nucleocapsid protein (as measured by Roche Elecsys) post-baseline, OR
    - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits)

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

6.4.5. Analysis for Secondary Endpoints on Efficacy

The SARS-CoV-2 infections and asymptomatic SARS-CoV-2 infections will be analysed using the same methods described for the analysis on primary efficacy endpoints, i.e. the

stratified Cox proportional hazard model with Efron's method of tie, and the estimate of rVE and its 95% CI will be provided. The censoring rule in Table 4 will be followed.
The SARS-CoV-2 infection incidence rates will be provided by each treatment group for SARS-CoV-2 infections and asymptomatic SARS-CoV-2 infections separately, calculated as the number of events divided by the total person-time.
Summaries of person-time and incidence rate, and 95% CI for incidence rate, will be performed by treatment group. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time described in Section 6.4.3.
Infection incidence rate will also be provided by age group.

6.4.6. Sensitivity Analyses

Following sensitivity analyses will be performed:

- The analysis for primary efficacy endpoint will be performed based on protocol-defined COVID-19 (secondary definition).
- The primary endpoints will be performed based on cox proportional hazard model including study vaccination group as a fixed effect, adjusted by stratification factor age group at randomization (≥12 to <18 years, ≥18 to <65 years, or ≥65 years) and additional factors SARS-CoV-2 status at pre-injection, number of prior COVID-19 doses, and type of last prior COVID-19 vaccine if applicable.
- To assess impact of off-study COVID-19 use on rVE estimate, for participant who take off-study COVID-19 vaccine, participants data after off-study COVID-19 vaccine use will not be censored (Table 4).
- Instead of positive RT-PCR test, consider either positive antigen test or positive RT-PCR test or positive multiplex SARS-CoV-2 test, the other derivation stays the same. This sensitivity analysis is to assess potential COVID-19 cases loss if participants failed to obtain protocol required RT-PCR test.

  - Modified CDC defined COVID-19 case definition (based on either positive antigen test or positive RT-PCR test)
  - Modified protocol defined COVID-19 case definition (based on either positive antigen test or positive RT-PCR test)

- The rVE of mRNA-1283 as compared to mRNA-1273 [variant formulation] to prevent first COVID-19 event starting after study vaccine injection.
  - CDC defined COVID-19 case definition
  - Protocol defined COVID-19 case definition

- Instead of later date of the two (RT-PCR test and symptom), consider earlier date of the two (RT-PCR test and symptom) as the date of the definition of COVID-19, the other derivation stays the same.
  - CDC defined COVID-19 case definition
  - Protocol defined COVID-19 case definition

The sensitivity analyses will be analysed using the same methods described for the analysis on primary efficacy endpoints, i.e. the stratified Cox proportional hazard model with Efron's method of tie, and the estimate of rVE and its 95% CI will be provided. The censoring rule in Table 4 will be followed.

In addition, rVE will be analyzed using the exact method described in Section 6.4.3. Summaries of person-time and COVID-19 incidence rate, and 95% CI for incidence rate, will be performed by treatment group (mRNA-1283 [variant formulation] 10 µg vs mRNA-1273 [variant formulation] 50 µg) for each sensitivity analysis. 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time as described in Section 6.4.3.

6.4.7. Analysis for Exploratory Efficacy Endpoint

For SARS-CoV-2 infections that with available sequencing data, summary of SARS-CoV-2 infections by variants may be provided.

6.4.8. Subgroup Analysis

To assess consistency of rVE across various subgroups, subgroup analyses of the primary efficacy endpoint will be performed in select subgroups specified in Section 6.1.9 based on the PPSE. The primary efficacy endpoint will be analysed by each of the subgroups using the same methods described for the primary efficacy endpoint analysis, i.e. the stratified Cox proportional hazard model with Efron's method, and the estimate of rVE and its 95% CI will be provided within each category.

If the number of participants in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses. Forest plots will be provided for rVE and its 95% CI for the subgroup analyses based on PPSE.

6.5. Safety Analysis

Safety and reactogenicity will be assessed by a clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, vital sign, and physical examination findings.

Unsolicited AEs will be coded by SOC and PT according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) is used in this study with modifications for solicited ARs as presented in Table 7 of the study protocol.

All safety endpoints will be analyzed for all participants in both Part 1 and Part 3.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be performed by the treatment group defined in Section 6.1.7 unless otherwise specified.

For Part 1, COVID-19 and SARS-CoV-2 infections (symptomatic or asymptomatic) are specified efficacy endpoints. Confirmed and suspected COVID-19 will not be counted as unsolicited AEs even if it meets serious criteria.

For Part 3, COVID-19 and SARS-CoV-2 infections are not considered efficacy endpoints; therefore, confirmed and suspected COVID-19 events will be counted as unsolicited AEs.

Solicited AR will only be counted as unsolicited AE when it meets serious criteria.

6.5.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. [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 (HCP).

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by vaccination group (up to 28 days after injection and throughout the study follow-up period)).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for unsolicited AEs with numbers of participants included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1283 and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if participants reported multiple events under the same SOC and/or PT.

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

6.5.1.1. Incidence of Adverse Events

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

- Any unsolicited AEs
- Any serious AEs
- Any fatal AEs
- Any unsolicited medically-attended AEs
- Any unsolicited AEs leading to discontinuation from study
- Any unsolicited severe AEs
- Any Non-Serious AEs
- Any AESI

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

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

6.5.1.2. AEs by System Organ Class and Preferred Term

The following summary tables of AEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited AEs
- All unsolicited AEs that are treatment-related
- All serious AEs
- All serious AEs that are treatment-related

- All unsolicited AEs leading to discontinuation from study
- All unsolicited Severe AEs
- All unsolicited Severe AEs that are treatment-related
- All unsolicited medically-attended AEs
- All unsolicited medically-attended AEs that are treatment-related
- All AESI
- All AESI that are treatment-related

6.5.1.3.AEs by Preferred Term

A summary table of all unsolicited AEs by PT will be provided. PTs will be sorted in a descending order according to the frequency in mRNA-1283 group.

6.5.1.4. AEs by System Organ Class, Preferred Term and Severity

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

- All unsolicited AEs
- All unsolicited AEs that are treatment-related

6.5.1.5.Subgroup Analysis of AEs

An overview of AE, AE summaries presented by SOC and PT will be provided for the selected subgroups defined in Section 6.1.9.

6.5.2. Solicited Adverse Reactions

Solicited ARs are selected signs and symptoms that participants are asked to record/report after receipt of the investigational product. In this study, the solicited ARs are reactogenicity events. The term “reactogenicity” refers to the occurrence of solicited adverse reactions associated with vaccine administration. The eDiary will solicit daily

participant reporting of ARs using a structured checklist (protocol Section 8.3.5). Participants will record such occurrences in the eDiary on the day of each study injection and the 6 subsequent days.

The following local ARs will be solicited by the eDiary: Injection site pain, Injection site erythema (redness), Injection site swelling/induration (hardness), and Axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), Arthralgia (joint aches in several joints), nausea/vomiting, chills, and fever (oral),

The solicited ARs will be graded based on the grading scales presented in Table 7 in protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

Analyses of solicited ARs will be provided by treatment group based on Solicited Safety Set, unless otherwise specified.

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

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

The onset of individual solicited AR is defined as the time point after the injection at which the respective solicited AR first occurred. The number and percentage of

participants with onset of individual solicited AR will be summarized by treatment group, study day relative to the corresponding injection (Day 1 through Day 7).

The number of days will be calculated as the end date of the solicited AR -start date of the solicited AR+1 for solicited AR that occurred within the 7 days of injection including the day of injection, no matter it is intermittent or continued.

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

The above analyses of solicited ARs will be provided for the selected subgroups defined in Section 6.1.9.

6.5.3. Pregnancy Tests

A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before injection. 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.

6.5.4. Vital Sign

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria (DHHS 2007) will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 2 or higher abnormality at any post injection visit, then all results of vital sign measurement for that subject will be presented in the listing.

6.6. Other Exploratory Analysis

Exploratory analyses described in this section will not be performed at the interim analyses and may be performed at the primary analysis.

- Descriptive summaries of GMs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection
    - GM antibody levels against emerging SARS-CoV-2 variants with corresponding 95% CI.
    - GMFR of postbaseline/baseline antibody levels against emerging SARS-CoV-2 variants with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.
    - The number and percentage of participants with seroresponse (primary and secondary definition Section 4.2.1) at all planned timepoints after study injection will be provided by treatment group with 2-sided 95% CI using Clopper-Pearson method.
- Characterize the SARS-CoV-2 genomic sequence of viral isolates
- Evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19 (a standalone SAP may be developed to assess these endpoints)

6.7. Data Safety Monitoring Board (DSMB)

An independent DSMB will periodically review blinded and unblinded data, including both safety data and events of SARS-CoV-2 infection and COVID-19 at scheduled data review meetings.

After each data review meeting or interim analysis, the DSMB will make a recommendation to the Sponsor to take one of the following courses of action:

- Pause further enrollment due to a safety concern.
- Pause enrollment and consider a change in study design.
- Continue enrollment and/or study conduct as planned.
- Review the rVE interim data based on the prespecified decision rules regarding Part 2 enrollment (Section 4.3).

The Sponsor may also request that the DSMB conduct ad hoc reviews of safety events from this study or other data, including new nonclinical or clinical information related to study intervention external to this study. The DSMB will review all available study data to adjudicate such events in accordance with the DSMB charter.

The DSMB composition, its remit, and frequency of data review will be further defined in the DSMB charter.

6.8. Planned Analysis

6.8.1. Interim Analysis

The planned interim analyses include: 1): Part 1 safety and immunogenicity interim analysis (IA 1); 2): Part 1 rVE interim analysis (IA2); 3): rVE primary analysis (Part 1 and Part 2 combined) if Part 2 enrollment occurs (IA 3[3]); 4): Japan cohort interim analysis and 5): Part 3 interim analysis.

An interim analysis (IA1) of safety and immunogenicity was performed after a subset of participants of Part 1, had been followed up for at least 29 days after the injection.

IA1 focused on safety and immunogenicity data. There were no COVID-19 incidence rate nor SARS-CoV-2 incidence rate summaries for the first IA. There were also no COVID-19 or SARS-CoV-2 infection subject incidence AE summary tables since these cases were mapped out of AE dataset.

To keep sponsor blinded to COVID-19 efficacy data, NJSTAT unblinded biostatistician/unblinded programmer did not deliver IA1 unblinded datasets (SDTM, ADaM) to the Sponsor biostatistician/programmer. Details of unblinding level to the prespecified Sponsor unblinded team were documented in the mRNA-1283-P301 Data Blinding Plan version 1.0 dated 27 Nov 2023.

[3] Given that early efficacy from the Part 1 rVE interim analysis (IA2) was met, the Part 2 enrollment did not occur as an outcome of adaptive study design, this IA is no longer applicable.

An interim analysis (IA2) for rVE will be performed when Part 1 accrues at least 700 COVID-19 events. DSMB will review unblinded results and make a recommendation to Sponsor based on pre-specified rules (see section 4.3). The Sponsor will be blinded. Data blinding was documented in Data Blinding Plan Version 2.0 dated 23 Feb 2024.

The purpose of this interim analysis was to assess whether the target number of COVID-19 events need to be increased from 2087 (rVE mRNA-1283 vs mRNA-1273: 3%) to 3500 (rVE mRNA-1283 vs mRNA-1273: 0) to ensure adequate power for the rVE objective. Early success and futility were also be assessed at this interim analysis. The Lan-DeMets O'Brien-Fleming approximation spending function was used for efficacy to preserve the (1-sided) 0.025 false positive error rate over IA2 and primary efficacy analyses. The Lan-DeMets O'Brien-Fleming approximation spending function method was also be used for futility boundary. Table 6 provides examples of efficacy and futility boundaries based on various information fraction (# of events) at interim if target rVE is 3% (mRNA-1283 vs mRNA-1273).

Table 6 Efficacy and Futility Boundary (Assuming rVE $_{1283 \text{ vs } 1273}$ of 3%, N=2087)

Information Fraction at IA	Number of Events at IA	Efficacy Boundary Z scale	Futility Boundary Z scale
0.3	626	-3.929	0.496
0.35	730	-3.614	0.179
0.4	835	-3.356	-0.097
0.45	939	-3.144	-0.338
0.48*	1002	-3.031	-0.471
0.5	1044	-2.962	-0.555
0.55	1148	-2.806	-0.751
0.60	1252	-2.669	-0.931

*Total number of cases (2087) planned was based on part 1 rVE IA occurred at ~1000 cases. Boundary calculation was performed in EAST6.5

Given that early efficacy from the Part 1 rVE interim analysis (IA2) was met, the DSMB recommended not enrolling Part 2. The rVE primary analysis for Part 1 and Part 2 combined will not be performed.

For Part 3, and for the Japan cohort, an interim analysis will be performed when all participants have been followed up for at least 29 days after the injection. Unplanned interim analyses may be performed based on the separate requests (eg, regulatory agencies).

6.8.2. Final Analysis

The final analysis of all endpoints will be performed after participants have completed all planned study procedures in each study part. Results of the final analysis will be presented in the clinical CSR, including individual listings.

6.9. Multiplicity Adjustments

The overall type I error rate for this study is strictly controlled at 0.025 (one-sided). The immunogenicity endpoints and rVE endpoint will be tested based on prespecified sequential testing strategy. The hypothesis for the rVE endpoint will be tested based on CDC-defined COVID-19 if all 4 co-primary immunogenicity endpoints are met (Figure_1).

The overall Type I error rate for the rVE analysis at the IA (IA2) and the primary rVE analysis (Part 1 and Part 2 combined if Part 2 enrollment occurs, IA3), is strictly controlled at 0.025 (1-sided) based on the Lan-DeMets O'Brien-Fleming approximation spending function.

For the adaptive sample size re-estimation, if the recommended target number of COVID-19 events after the Part 1 rVE interim analysis (IA2) remains at 2087 events (initially planned number of events assuming rVE of 3% [mRNA-1283 vs mRNA-1273]), the hypothesis testing H_0: rVE $\leq$ -10% can be evaluated directly based on the lower bound of alpha-adjusted CI of rVE. If rVE lower bound >-10% (this is equivalent to the upper bound of the alpha-adjusted CI of the HR <1.1), non-inferiority of preventing the first occurrence of COVID-19 of mRNA-1283 injection compared to mRNA-1273 will be demonstrated at one-sided alpha of 0.025.

If the DSMB recommendation is to increase the number of COVID-19 events from 2087 to 3500 (number of events needed assuming rVE of 0 [mRNA-1283 vs mRNA-1273]), the CHW Test (Cui L 1999; Lehmacher 1999) will be used for hypothesis testing at the primary rVE analysis (Part 1 and Part 2 combined) to preserve the type I error rate.

$$Z^*_{2,chw} = \sqrt{\frac{n_1}{n_2}} Z_1 + \sqrt{\frac{\tilde{n}_2}{n_2}} Z^*_2$$

$$Z^*_2 = (Z_{overall,unadjusted} - \sqrt{\frac{n_1}{n^*_2}}\, Z_1) / \sqrt{\frac{\ddot{n}^*_2}{n^*_2}}$$

Where n_1 is the number of events observed in the Part 1 rVE interim analysis (IA2), and the sum of n_1 and $\tilde{n}_2$equals to the original planned number of events (2087 events); $\tilde{n}_2 = n_2 - n_1$; n^*_2 is the total number of COVID-19 events that DSMB recommended (3500 events) based on prespecified criteria ($0.35 \leq$ conditional power < 0.8); $\ddot{n}^*_2 = n^*_2 - n_1$ (incremental number of events between Part 1 rVE interim analysis [IA2] and primary rVE analysis [Part 1 and Part 2 combined if Part 2 enrollment occurs, IA3]); and $Z_1$is the test statistics at the Part 1 rVE interim analysis.

Due to early efficacy success from the Part 1 rVE interim analysis (IA2), Part 2 was not enrolled.

7. Changes from Planned Analyses in Protocol

RT-PCR confirmed SARS-CoV-2 infection

For Part 1 and Japan cohort, differing from protocol section 8.3.6, RT-PCR confirmed COVID-19 cases will not be counted as MAAEs. For Part 1 and Japan cohort, any SARS-CoV-2 infection will not be counted as AE even if it meets serious criteria.

Solicited ARs during a 7-day follow-up period after the study injection

Differing from protocol section 8.4.6, a solicited adverse reaction will only be counted as unsolicited AE when it meets serious criteria.

8. References

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Protocol mRNA-1283-P301 A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283.222 administered as a booster dose compared with mRNA-1273.222 in participants aged 12 years and older for the prevention of COVID-19 Immunogenicity Data Sampling Plan Version 3. 21 Aug 2023.

Protocol mRNA-1283-P301 A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative efficacy of mRNA-1283.222 administered as a booster dose compared with mRNA-1273.222 in participants aged 12 years and older for the prevention of COVID-19 Data Blinding Plan (DBP) Version 1.0. 27 Nov 2023.

Protocol mRNA-1283-P301 A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative efficacy of mRNA-1283 administered as a booster dose compared with mRNA-1273 in participants aged ≥12 years for the prevention of COVID-19 Data Blinding Plan (DBP) V2.0. 23 Feb 2024.

9. List of Appendices

9.1. Appendix A Standards for Variable Display in TFLs

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

Categorical Variables: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

9.2. Appendix B Analysis Visit Windows

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

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

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 7 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 7 Analysis Visit Windows

Visit	Target Study Day	Visit Window in Study Day
Nasopharyngeal swab (or saliva)		
Day 1	1 (Date of Injection)	1, Pre-dose
Day 29 (Month 1)	29	[2, 60]
Day 91 (Month 3)	91	[61,136]
Day 181 (Month 6)	181	[137, 273]
Day 365 (Month 12)	365	≥274
Immunogenicity		
Day 1	1 (Date of Injection)	1, Pre-dose
Day 29 (Month 1)	29	[2, 60]
Day 91 (Month 3)	91	[61,136]

Day 181 (Month 6)	181	[137, 273]
Day 365 (Month 12)	365	≥274

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

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

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

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

Table 8 Prior, Concomitant, and Post Categorization of Medications

Medication Start Date	**Medication Stop Date**		
	< Injection Date of IP	**≥ Injection Date and ≤ 28 Days After Injection**	**> 28 Days After Injection [2]**
< Injection date of IP [1]	P	P, C	P, C, A
≥ Injection date and ≤ 28 days after the injection	-	C	C, A
> 28 days after injection	-	-	A

A: Post; C: Concomitant; P: Prior

Non-study Vaccinations and Off-Study Covid-19 Vaccine is considered prior if start date is before injection date of IP and is considered as concomitant if medication start date and end date are completely missing.

[1] includes medications with completely missing start date

[2] includes medications with completely missing end date

9.4. Appendix D Imputation Rules for Missing Dates of AEs

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

1. Missing or partial start date:
    - If only Day is missing, use the first day of the month, unless:
        - The AE end date is on/after the date of injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of injection, even if AE time was collected.
    - If Day and Month are both missing, use the first day of the year, unless:
        - The AE end date is on/after the date of injection or is missing/partial AND the start year of the AE coincides with the start year of the injection. In this case, use the date and time of injection, when time is available.
    - If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered occurring during the study.
2. Missing or partial end dates will not be imputed.

9.5. Appendix E Schedule of Events

Please refer to Table 1 in Section 1.3 Schedule of Assessments in the protocol.

9.6. Appendix F Estimands and Estimand Specifications

Table 9 Intercurrent Event Types

Label	Intercurrent Event Type	Comment
IcEv1 (early discontinuation or death without confirmation of cases, ie, unrelated death)	Early discontinuation from study preventing from confirmation of COVID-19, ie, unrelated death or withdrawal consent prior to confirmed COVID-19	Participants in PPSE who withdraw consent or die due to reasons unrelated to COVID-19 without confirmation of being a case will all be included in primary efficacy analysis and censored by intercurrent event strategy.
IcEv2 (early COVID-19)	COVID-19 starting up to 14 days after the injection	Participants in PPSE who experience an early COVID-19 up to 14 days after the injection will all be included in primary efficacy analysis and censored by intercurrent event strategy.
IcEv3 (off-study COVID-19 vaccine use)	off-study COVID-19 vaccine use	Participants in PPSE who take off-study Covid-19 vaccine will all be included in primary efficacy analysis and censored by intercurrent event strategy.

Abbreviation: IcEv: intercurrent event, PPSE: Per-Protocol Set for Efficacy

Table 10 Primary Estimand for rVE Primary Objective

Objective: To demonstrate the non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulation) to prevent COVID-19	
Estimand Description	rVE will be measured using 1 – HR (mRNA-1283/mRNA-1273 [variant formulation]) of COVID-19 from 14 days after injection. A hypothetical strategy will be used for deaths unrelated to COVID-19 and early COVID-19 in participants in the PPSE. While-on-treatment strategy will be used for participants taking an off-study COVID-19 vaccine during the study.
Target Population	Medically stable individuals, ages 12 and above. The population excludes those who received a COVID-19 vaccine within 90 days prior to enrollment or had positive SARS-CoV-2 testing by an authorized/approved lateral flow/rapid antigen or PCR within 90 days prior to enrollment. Participants with chronic diseases requiring ongoing medical intervention or within the last 2 months prior to enrollment will be excluded. Participants with immunocompromising conditions or medications, or malignancy within 5 years (excluding nonmelanoma skin cancer) will be excluded.
Variable/Endpoint	Time to first COVID-19, censoring at early discontinuation, early COVID-19, off-study COVID-19 vaccine use, or last assessment for an event not being observed, whichever occurs earlier.

Objective: To demonstrate the non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulation) to prevent COVID-19	
Treatment Condition(s)	Test: mRNA-1283 (variants formulation) Reference: mRNA-1273 (variants formulation)
Estimand Label	**Estimand 1**
Population-Level Summary	rVE defined as 1 - HR of mRNA-1283/mRNA-1273
Intercurrent Event Strategy	
IcEv1 (death unrelated to COVID-19)	Hypothetical
IcEv2 (early COVID-19)	Hypothetical
IcEv3 (off-study COVID-19 vaccine use)	While on treatment strategy
Rationale for Strategy(s)	Hypothetical: unrelated death without confirmation of COVID-19 will be censored at the time of death as if there is no event, handled with independent censoring. Hypothetical: early event (events occurring prior to 14 days after study vaccine injection) in PPSE will be censored at the time of event onset as if it is not an event, handled with independent censoring. While on treatment strategy: for participants who take off-study COVID-19 vaccine, participants will be censored at the time of off-study COVID-19 vaccine use.

9.7. Appendix G Observed rVE And Corresponding Conditional Power at Interim (Assume Study Accumulated ~1000 Cases At rVE Interim Analysis [IA2])

Table 11 Observed rVE and Corresponding Conditional Power at Interim Analysis [IA2]

Observed rVE	Conditional Power
5%	97%
4%	94%
3%	89%
2%	82%
1%	73%
0%	62%
-1%	49%
-2%	37%
-3%	26%
-4%	17%
-5%	10%

Note: 2087 total cases needed (assume rVE=3%) if case number equal to ~1000 at rVE interim analysis (IA2)

9.8. Appendix H Country Specific Requirements - Japan

The Japan study design mirrors the global study with the approved VOC for 2023/2024 respiratory season. The objectives of this study are to evaluate the safety and immunogenicity of mRNA-1283.815 compared to mRNA-1273.815 in approximately 692 Japanese participants. The study population is in addition to the global protocol. Planned analyses for Japan specific items are outlined in this Appendix based on Section 10.7 of the approved clinical study protocol (CSP) Amendment 2 JPN-2 dated 19-Jan-2024.

1. Japan Study Objectives (Section 2)

The primary objective of the Japan cohort is to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1283.815 compared to mRNA-1273.815 in Japanese participants.

1.1. Primary Objectives

The primary objectives are the following:

- To demonstrate a non-inferior antibody response of mRNA-1283.815 10 µg compared to the antibody response of mRNA-1273.815 50 µg in the Japan cohort based on GMR at Day 29 after the booster dose.
- To evaluate the safety and reactogenicity of mRNA-1283.815 10-µg booster dose.

1.2. Secondary Objectives

- To characterize the antibody response against Omicron XBB.1.5 and the ancestral SARS-CoV-2 D614G (mRNA-1283.815) at all study timepoints.

1.3. Exploratory Objectives

- To assess the incidence of COVID-19 and asymptomatic SARS-CoV-2 infection in Japan cohort who receive mRNA-1283.815 or mRNA-1273.815.

2. Japan Study Endpoints (Section 3)

2.1. Primary Endpoint

Immunogenicity Endpoint

- GMR of Omicron XBB.1.5 GM in the Japan cohort who received mRNA-1283.815 10 µg over the Omicron XBB.1.5 GM in the Japan cohort who received mRNA-1273.815 50 µg at Day 29 after the booster dose.

Safety Endpoints

- Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after the booster dose.
- Unsolicited AEs during the 28-day follow-up period after the booster dose.
- SAEs, MAAEs, AEs leading to withdrawal, AESIs from Day 1 to EoS.

2.2. Secondary Endpoints

- Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G GMs at all planned timepoints (Day 91, Day 181, and Day 365).
- SRR (primary and secondary definition Section 4.2.1) against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G at all planned timepoints.

2.3. Exploratory Endpoints

COVID-19:

  - CDC-defined COVID-19 case definition (primary definition)
  - Protocol-defined COVID-19 case definition (secondary definition)

SARS-CoV-2 infection, Asymptomatic SARS-CoV-2 infection

3. Study Design (Section 4)

In addition to the global enrollment, approximately 692 Japanese participants will enroll in the Japan cohort across clinical trial sites in Japan. Participants will be randomized in a 1:1 ratio to mRNA-1283.815 or mRNA-1273.815. This will be an observer-blinded study.

The Japan cohort will target age groups (12 to <18, 18 to <65, and ≥65 years) that are approximately similar in proportion to the global study population.

3.1. Statistical Hypothesis for the Japan Cohort (Section 4.2)

The null hypothesis H0: Antibody GM level against Omicron XBB.1.5 after the mRNA-1283.815 booster dose (10 µg) in the Japan cohort is inferior to that after mRNA-1273.815 booster dose (50 µg) in the Japan cohort, based on the GMR defined as the ratio of GM level against Omicron XBB.1.5 of mRNA-1283.815 at Day 29 vs the GM level against Omicron XBB.1.5 of mRNA-1273.815 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).

The non-inferiority in the GMR at Day 29 after mRNA-1283.815 booster dose (10 µg) in the Japan cohort against XBB.1.5 compared to mRNA-1273.815 booster (50 µg) in the Japan cohort against the same variant will be demonstrated if the lower bound of 2-sided 95% CI of GMR >0.667.

3.2. Sample Size and Power (Section 4.3)

The Japan cohort will use mRNA-1273.815 (50 µg) as the comparator for the Japan cohort primary immunogenicity objective. Assuming the true GMR against XBB.1.5 at Day 29 (mRNA-1283.815 vs. mRNA-1273.815) is 1, a standard deviation of natural log transformed level of 1.8, and a non-inferiority margin for GMR of 1.5, approximately 622 evaluable participants (311:311 for mRNA-1283.815 vs. mRNA-1273.815) in the Japan cohort are required. This provides approximately 80% power to demonstrate non-inferior antibody responses of mRNA-1283.815 vs. mRNA-1273.815 in the Japan cohort for primary endpoint at 2-sided alpha of 0.05. It is also expected that ~10% participants might be excluded from the PPIS (eg, reasons such as missing immunogenicity samples); hence the Japan cohort requires 692 participants (346 participants per arm).

4. Analysis Sets (Section 5)

Analysis Sets include both PPIS and PPSE for Japan cohort, alongside the Randomization Set, Full Analysis Set, Solicited Safety Set and Safety Set as described in Section 5.

Per-Protocol Immunogenicity Set (PPIS)

The Per-protocol immunogenicity set (PPIS) for Japan cohort consists of all participants from the Japan cohort in the FAS who receive the planned dose of study vaccination, have

baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data and have no major protocol deviations that impact key or critical data. The PPIS will be the primary analysis set for analyses of immunogenicity unless otherwise specified.

Per-Protocol Set for Efficacy (PPSE)

The Per-Protocol Set for Efficacy (PPSE) for Japan cohort consists of all participants in the FAS who receive the planned dose of IP and have no major protocol deviations that impact vaccine efficacy data. Participants will be analyzed according to their randomized study arm.

5. Statistical Analysis (Section 6)

All country-specific analyses for Japan Cohort will adhere to statistical analysis in Section 6 of the study SAP unless explicitly stated otherwise in the appendix H. All analysis will be performed by treatment group (mRNA-1283.815 10 µg, mRNA-1273.815 50 µg) if applicable.

5.1. General Considerations

The PPIS is the primary analysis population used in the immunogenicity analyses and the PPSE is the primary analysis population used in the efficacy analyses, unless otherwise specified. Subjects will be included in the treatment group to which they were randomized.

Safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. Subjects will be included in the treatment group to which they actually received.

Treatment Groups (Section 6.1.7)

The following treatment groups from Japan Cohort will be used for summary purposes:

- mRNA-1283.815 10 µg
- mRNA-1273.815 50 µg

Subgroup (Section 6.1.9)

Safety, efficacy and immunogenicity endpoints may be analyzed in selected subgroups if applicable, including but not limited to, the following subgroups:

- Sex (Female, Male)
- Age (≥12 to <18 Years, ≥18 to <65 Years, ≥65 Years)
- Baseline SARS-CoV-2 Status (Positive, Negative)
- Number of prior COVID-19 booster doses (0, 1, 2, ≥3)
- Number of prior COVID-19 vaccine doses
- Type of last prior COVID-19 vaccines (mRNA original monovalent, mRNA Omicron bivalent, non-mRNA vaccine, non-mRNA vaccine)
- Dosing interval group (Date of current dose – date of last prior dose of COVID-19 vaccine +1) (months): (e.g. ≥/< median, or by quartiles)

If the number of participants in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses.

5.2. Background Characteristics

Demographics and Baseline Characteristics (Section 6.2.2)

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

The number and percentage of subjects will be provided for below baseline characteristics:

- Baseline SARS-CoV-2 status (Positive, Negative)
- Number of prior COVID-19 booster doses (0, 1, 2, ≥3)
- Number of prior COVID-19 vaccine doses

- Dosing interval group (Date of current dose – date of last prior dose of COVID-19 vaccine +1) (months): (e.g. ≥/< median, or by quartiles)
- Type of last prior vaccine: mRNA original monovalent, mRNA Omicron bivalent, non-mRNA vaccine

The summaries will be provided based on the Safety Set. The summaries may be performed using PPIS or PPSE if number of participants in these analysis sets differ more than 5% compared to that of Safety Set

5.3. Immunogenicity Analysis (Section 6.3)

The Sampling of the Immunogenicity Subset are not applicable for the Japan cohort.

5.3.1. Analyses for the Primary Immunogenicity Objectives

The primary objective is to demonstrate a non-inferior antibody response (shown by pseudotyped virus neutralizing antibody GM level) of mRNA-1283.815 10 µg in the Japan cohort compared to mRNA-1273.815 50 µg in the Japan cohort against Omicron XBB.1.5 at Day 29.

An analysis of covariance model (ANCOVA) will be carried out with the dependent variable of the Omicron XBB.1.5 GM level (definition in Section 6.1.6) at Day 29 and a group variable (mRNA-1283.815 vs. mRNA-1273.815 in the Japan cohort) as the fixed effect, adjusted by SARS-CoV-2 status at baseline, and age group per randomization. The number of prior COVID-19 boosters, and type of last prior COVID-19 booster may be included in the model if applicable. The GM will be estimated by the geometric least square mean (GLSM) from the model. The serum antibody GMR at Day 29 (mRNA-1283.815 vs. mRNA-1273.815 in the Japan cohort) will be estimated by the ratio of GLSM. The GMR and its 2-sided 95% CI will also be provided to assess the difference in antibody response between mRNA-1283.815 and mRNA-1273.815 in the Japan Cohort. The decision rules for the hypothesis testing of the GMR of Omicron XBB.1.5 (mRNA-1283.815 vs mRNA-1273.815), ie, non-inferiority criteria, will be implemented. If the lower bound of the 95%

CI of the GMR is >0.667, non-inferiority of serum antibody GM of mRNA-1283.815 booster dose compared to mRNA-1273.815 will be considered demonstrated based on GMR.

Similar analysis will be performed for ancestral SARS-CoV-2 D614G GM as descriptive analysis.

5.3.2. Analysis for the Secondary Immunogenicity Objectives

GM, GMFR of nAb level

Data from quantitative SARS-CoV-2-specific nAb value will be analyzed as below and summarized by treatment group, at each timepoint that an assessment is performed.

- GM of nAb levels against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G with corresponding 95% CI at each planned time point.
- GMFR of postbaseline/baseline nAb levels against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1.

The 95% CIs will be calculated based on the t-distribution of the log-transformed values for GM, and the difference of log-transformed values for GMFR, then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, Q1, Q3, minimum (min) and maximum (max).

The proportion of subjects with geometric mean fold-rise ≥ 2, and fold-rise ≥ 4 of serum SARS-CoV-2 specific nAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs.

In addition, GM of SARS-CoV-2-specific nAb levels with corresponding 95% CI will be plotted at each timepoint.

Seroresponse Analysis

The number and percentage of participants with seroresponse (based on two definitions described in Section 4.2.1) due to the booster at all planned timepoints will be provided

with 2-sided 95% CI using Clopper-Pearson method, based on nAb value against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G separately. The SRR differences at each visit due to the booster with their 95% CI (using Miettinen-Nurminen score method) between the 2 treatment groups at each visit will be tabulated.

At the final analysis, a sensitivity analysis will be performed for the immunogenicity endpoints by excluding immunogenicity data from participants after they have had a SARS-CoV-2 infection.

5.4. Efficacy Analysis (Section 6.4)

The incidence of COVID-19, SARS-CoV-2 infection, and asymptomatic SARS-CoV-2 infection are exploratory endpoints in the Japan cohort.

Efficacy analyses will be performed primarily based on PPSE. Participants will be included in the treatment group to which they are randomized.

5.4.1. CDC/ Protocol-Defined COVID-19

The definition of CDC/ Protocol-defined COVID-19 is provided in Section 6.4.1.

The number and percentage of participants who had an event (i.e. the first occurrence of COVID-19 starting after the injection) and participants who were censored will be summarized, for event censored for off-study COVID-19 vaccine use and regardless of off-study COVID-19 vaccine use, separately. The censoring rules of cases are outlined in Table 4.

Summaries of person-time and incidence rate, and 95% CI for incidence rate, will be performed by treatment group. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time described in Section 6.4.3

5.4.2. SARS-CoV-2 Infection (Symptomatic or Asymptomatic) /Asymptomatic SARS-CoV-2 Infection

The definition of SARS-CoV-2 infection (symptomatic or asymptomatic) and asymptomatic SARS-CoV-2 infection are separately provided in Section 6.4.4.1 and Section 6.4.4.2.

Summaries of SARS-CoV-2 infection regardless of symptomatology/asymptomatic SARS-CoV-2 infection will be conducted in a manner similar to that of the COVID event, except the first occurrence of SARS-CoV-2 infection will be used for the summary.

5.5. Safety Analysis (refer to Section 6.5)

For Japan cohort, COVID-19 and SARS-CoV-2 infections (symptomatic or asymptomatic) are specified efficacy endpoints. Confirmed and suspected COVID-19 will not be counted as unsolicited AEs even if it meets serious criteria.

6. Planned Analysis (Section 6.8)

6.1. Interim Analyses

An interim analysis of safety and immunogenicity will be performed after all Japan participants have been followed up for at least 29 days after the injection.

Unplanned interim analyses may be performed based on the separate requests (e.g., regulatory agencies).

6.2. Final Analysis

The final analysis of all endpoints will be performed after participants have completed all planned study procedures. Results of this analysis will be presented in a clinical CSR, including individual listings.

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