CLINICAL STUDY PROTOCOL

Protocol 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
Protocol Number:	mRNA-1283-P301
Amendment Number:	3
Amendment Scope:	Global Amendment
Date:	20 Dec 2023
Compound:	mRNA-1283.222, mRNA-1283.815
Global Amendment 2 Approval Date:	08 Aug 2023
Global Amendment 1 Approval Date:	02 May 2023
Original Protocol Approval Date:	27 Feb 2023
Brief Title:	A study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants ≥12 years of age to prevent COVID-19
Study Phase:	Phase 3
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number(s):	IND: 27196 Pediatric Investigational Plan: EMEA-003426-PIP01-23

Sponsor Signatory: See e-Signature and date signed on last page of the document.

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "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" dated 20 Dec 2023 and the most recent version of the mRNA-1283 Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB/IEC approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB/IEC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	20 Dec 2023
Japan Country Amendment	12 Sep 2023
Amendment 2	08 Aug 2023
Amendment 1	02 May 2023
Original Protocol	27 Feb 2023

Amendment 3: 20 Dec 2023

This amendment is considered substantial because it adds 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.

Overall Rationale for the Amendment:

The rationale for the addition of Part 2 is to increase the total sample size to enable a pooled relative vaccine efficacy analysis with both study parts (Part 1 and Part 2). Up to approximately 33,574 participants in Part 1 and Part 2 combined will be enrolled to support the primary relative vaccine efficacy objective. The 2023/2024 COVID-19 variant vaccine sequence (Omicron XBB.1.5-containing study vaccines [mRNA-1283.815 or mRNA-1273.815]) will be used in Part 2.

Section # and Name	Description of Change	Brief Rationale
1.1 Protocol Synopsis and Title Page	Incorporated the amendment changes from the body text and clarified text.	Consistency within the document.
1.2 Study Schema	Revised to include the Part 2 study design including population, study treatment, and study assessments.	Provides a visual representation of the study design for Part 1 and Part 2.
1.3 Schedule of Assessments	Part 2 participants will use the eDiary to collect reactogenicity for adolescents and unvaccinated participants. Part 2 participants will not undergo testing for the presence of non-SARS-CoV-2 respiratory pathogens.	Sufficient reactogenicity information was collected in Part 1; therefore only subsets of participants in Part 2 will collect reactogenicity data. Sufficient testing for non-SARS-CoV-2 pathogens was performed in Part 1.

Section # and Name	Description of Change	Brief Rationale
2.1 Rationale 4.2 Scientific Rationale for the Study Design	Included evaluation of the mRNA-1283.815 in the safety, immunogenicity, and rVE of the study. Revised the purpose of the study to evaluate the rVE based on pooled analysis from Part 1 and Part 2.	The addition of Part 2 will support the primary rVE objective and the rVE non-inferiority comparison between mRNA-1283 and mRNA-1273 with a 10% margin.
2.2.4 mRNA-1283.815 2.2.5 mRNA-1273.815 6.1 Study Intervention Administered 6.2.1 Clinical Study Material Preparation	Added descriptions of the study vaccine (variant formulation) for Part 2.	Part 2 uses the variant formulation for the 2023/2024 season.
2.2.6 Nonclinical Studies	Updated information on mRNA-1283 animal challenge studies using NTD and RBD from XBB variants was added.	Provides updated nonclinical results for mRNA-1283.
2.3.1 Risk Assessment 2.3.3 Overall Benefit/Risk Conclusions	Administrative changes.	Clarified text for readability.
3. Objectives and Endpoints	Objectives and endpoints were added for Part 2. The rVE objective will be supported by pooled analysis with Part 1 and Part 2 combined. A secondary endpoint for the incidence of severe COVID-19 will be assessed in Part 2. It was clarified that the immunogenicity endpoints for Part 1 and Part 2 would be based on the neutralizing antibody response. A correlate of risk and protection from COVID-19 was also added in the exploratory objectives of Part 1 and Part 2.	The addition of Part 2 will support the primary rVE objective and the rVE non-inferiority comparison between mRNA-1283 and mRNA-1273 with a 10% margin. Additionally, the incidence rate of severe COVID-19 will be a secondary endpoint in Part 2. Immune response and rVE information in Part 1 and Part 2 will support the identification of correlates of risk and correlate of protection from COVID-19.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Described Part 2 as similar to Part 1 in study population apart from use of the 2023/2024 updated variant formulation in the study vaccines, and number of participants. Also, Part 2 will have no requirement for prior COVID-19 vaccination.	Increased the total study sample size to support the primary rVE objective. The study population in Part 2 will remove the requirement for prior COVID-19 vaccination to also evaluate mRNA-1283 in previously unvaccinated participants.
4.2 Scientific Rationale for the Study Design	Clarified the purpose of Part 1 and Part 2 as the rVE analysis.	The addition of Part 2 would support the non-inferiority rVE comparison with a 10% margin.
4.3 Justification for Dose	Added information on the 2023/2023 variant containing vaccines.	To address the different variant containing vaccines in the study.
4.4 End of Study Definition	Defined the EoS as the date the analyses are completed.	Template changed to ensure all data are available before the final database lock.
5. Study Population	Removed the enrollment numbers and stratification factors from this section.	Redundant with Section 4.1 Overall Design where enrollment numbers and stratification factors are provided.
5.1 Inclusion Criteria	Part 2 will not have a prior COVID-19 vaccination requirement. Proof of vaccination is still required for participants who previously received a COVID-19 vaccine.	To evaluate mRNA-1283 in previously unvaccinated participants.
6.2.3 Clinical Study Material Packaging and Labeling	Added descriptions of the study treatment (variant formulation) for Part 2. Minor corrections were made to the mRNA-1283.222 and mRNA-1273.222 descriptions.	Part 2 uses the variant formulation for the 2023/2024 season. Administrative change made to the mRNA-1283.222 and mRNA-1273.222 descriptions.
6.4 Blinding 9.1. Blinding and Responsibility for Analyses	Provided details regarding the blinding plan and included a DSMB review of interim rVE data from Part 1 prior to commencement of Part 2. The Sponsor will remain blinded to interim rVE analyses.	To provide clarification regarding the blinding and review of interim rVE data from the DSMB.

Section # and Name	Description of Change	Brief Rationale
8.2 Efficacy and Immunogenicity Assessment	rVE will be assessed for Part 1 and Part 2. Neutralizing antibody response is an exploratory objective in Part 2.	The addition of Part 2 will support the primary rVE objective and the rVE non-inferiority comparison between mRNA-1283 and mRNA-1273 with a 10% margin. The neutralizing antibody response is an exploratory objective in Part 2 given that the primary immunogenicity objective is prespecified in Part 1.
8.3 Safety Assessments 8.3.5 Use of Diaries 8.4.1 Time Period and Frequency for Collecting AE and SAE information. 8.4.2 Method of Detecting AEs and SAEs 8.4.6 Solicited ARs 9.5.2.2 Analysis for the Other Secondary Objective	Only Part 2 adolescents and previously unvaccinated participants will have reactogenicity assessments.	Sufficient reactogenicity was collected in Part 1. Since previously unvaccinated participants are a new population to this study, reactogenicity will be collected in these participants and in adolescents in Part 2.
8.3.6 Assessment for SARS-CoV-2 Infection	The definition of the secondary objective for severe COVID-19 was provided.	Severe COVID-19 is a secondary objective in Part 2.
9.2 Statistical Hypothesis	Revised the statistical hypothesis for rVE with a 10% margin and include both Part 1 and Part 2. Added the statistical analyses sets to be used for clarification.	The addition of Part 2 is required to support the rVE comparison with a 10% non-inferiority margin.
9.3 Sample Size Determination 9.5.2.1 Analysis for the Primary rVE Objective 9.6 Primary Estimands 9.8.1 Interim Analyses	Added rationale for the sample size of Part 2. Revised primary estimand for rVE. Distinguished the planned interim analyses. Added the decision rules for the DSMB recommendation based on rVE interim analysis.	The addition of Part 2 supports the rVE objective.
9.4 Analysis Sets 9.5.1.2 Analysis for the secondary and other immunogenicity objectives	The PPIS will be the primary analysis set for Part 1. A different analysis set may be used for the exploratory immunogenicity objective in Part 2.	The Part 1 immuno-subset has been prespecified as the group that will support the primary immunogenicity objective.

Section # and Name	Description of Change	Brief Rationale
9.5.2.2 Analyses for the Other Secondary Objective	Added the endpoint of severe COVID-19 in Part 2.	Evaluate severe COVID-19 occurring 14 days post injection.
9.6 Primary Estimands	Updated intercurrent event strategy for off-study COVID-19 vaccine use.	Participants will be censored from the time of off-study COVID-19 vaccine use to avoid potential confounding of the rVE results.
9.8.1 Interim Analysis	Specified the minimum number of COVID-19 events needed for a Part 1 rVE interim analysis and specified the requirements for an interim rVE analysis.	The addition of Part 2 will support the primary rVE objective and the rVE non-inferiority comparison between mRNA-1283 and mRNA-1273 with a 10% margin.
10.1.6.1 Data Safety Monitoring Board	Specified that the DSMB would also review interim rVE data and provide recommendations to the Sponsor based on prespecified decision rules.	The DSMB would review interim rVE information in a closed session and provide a recommendation to the Sponsor toward the sample size estimation for Part 2.
10.4 Appendix 4: Adverse Events of Special Interest	A Part 2 list of AESIs was added to reflect updates on AESIs.	The AESI list has updated to include capillary leak syndrome and to remove anosmia and ageusia associated with COVID-19.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
AxMP	auxiliary medicinal product
BA.4/5	BA.4/BA.5
bAb	binding antibody
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	Contract Research Organization
CSR	clinical study report
D	day
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG/EKG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMFR	geometric mean fold rise

Abbreviation	Definition
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	healthcare practitioner
HR	hazard ratio
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	legally authorized representative
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
N	number
nAb	neutralizing antibody
NIMP	non-investigational medicinal product
NP	nasopharyngeal
NTD	N-terminal domain
PCR	polymerase chain reaction
PEG2000-DMG	1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PP	per protocol

Abbreviation	Definition
PPE	personal protective equipment
PPIS	per protocol immunogenicity subset
PPSE	per protocol set for efficacy
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
SoA	schedule of assessments
S protein	spike protein
S-2P	spike protein with S-2P residues introduced for stability in a prefusion conformation
SRR	seroresponse rate
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia
VOC	variant of concern
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol 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

Brief Title:

A study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants ≥12 years of age to prevent COVID-19

Regulatory Agency Identifier Number(s):

Registry	ID
IND:	27196

Rationale:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged and are likely to continue to emerge. Some variants have the potential to circumvent immunity associated with previous infection or vaccination. Variants of concern are associated with increased infectivity and a reduction in the ability of convalescent sera or sera from vaccinated individuals to neutralize these emergent variants. To address the need for updated vaccination strategies, the Sponsor has used its messenger ribonucleic acid (mRNA)-based platform to develop a custom SARS-CoV-2 mRNA vaccine candidate, mRNA-1283, which encodes the N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike protein (S protein) of SARS-CoV-2. Animal challenge and protection studies have indicated protective responses elicited by RBD-based vaccines.

mRNA-1283 was designed with the objective of providing a longer shelf-life at refrigerated temperatures while having a safe and tolerable vaccine that can elicit immune responses which are comparable to the original vaccine, mRNA-1273, and at lower doses compared to mRNA-1273.

The Sponsor has previously evaluated mRNA-1283 and mRNA-1283.211 (contains equal mRNA amounts of the ancestral SARS-CoV-2 and Beta variant RBD and NTD) in a Phase 1 (mRNA-1283-P101) and Phase 2a (mRNA-1283-P201) study. In study P101, mRNA-1283 was administered as a 2-dose primary series (10, 30, 100 µg) in approximately 80 participants. mRNA-1283 was well tolerated as a primary series and elicited a similar or numerically higher nAb response against the ancestral SARS-CoV-2 D614G compared to an mRNA-1273 100 µg primary series comparator group, 28 days after completion of the primary series. In study P201, mRNA-1283 and mRNA-1283.211 were administered as a first booster dose (2.5, 5 and 10 µg) after immunization with the mRNA-1273 primary series in approximately 350 participants. The safety and reactogenicity profile of mRNA-1283 and mRNA-1283.211 were overall similar to a within-study 50 µg mRNA-1273 comparator. The immunogenicity results indicated that mRNA-1283 and mRNA-1283.211 elicited similar or numerically higher nAb responses against

the ancestral SARS-CoV-2 (D614G) and Beta (B.1.351) variants 28 days after the mRNA-1283 and mRNA-1283.211 booster doses.

Based on the previous evaluation of mRNA-1283 and mRNA-1283.211, the Sponsor has selected the 10-µg booster dose for the mRNA-1283.222 bivalent vaccine (contains equal amount of the ancestral SARS-CoV-2 and Omicron BA.4/BA.5 [BA.4/5] variant) as a dose with a favorable safety and reactogenicity profile, similar to the 50-µg booster dose of mRNA-1273 booster vaccine. Additionally, 10 µg of mRNA-1283 (including 10 µg of the bivalent vaccine Beta-containing mRNA-1283.211) elicited potent nAb responses against the ancestral SARS-CoV-2 D614G and the Beta variant (the variant contained in the vaccine) in the P201 study, 28 days after the booster dose.

The purpose of this study (Part 1 and Part 2) is to evaluate the rVE, safety, reactogenicity, and immunogenicity of mRNA-1283.222 vs mRNA-1273.222 (Part 1) and mRNA-1283.815 vs mRNA-1273.815 (Part 2). The non-inferiority of rVE analysis will be based on rVE data from Part 1 and Part 2, in a pooled analysis.

Objectives and Endpoints:

Part 1

Objectives	Endpoints
Primary	
• 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.	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[a] 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[a] difference of ancestral SARS-CoV-2 D641G between mRNA-1283.222 10 µg and mRNA-1273.222 50 µg at Day 29.
To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.	rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent the first event of COVID-19 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

Objectives	Endpoints
	– A positive RT-PCR test on a respiratory sample. • 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 for SARS-CoV-2 by RT-PCR.
To evaluate the safety and reactogenicity of 10 µg mRNA-1283.222.	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period. • Unsolicited AEs during the 28-day follow-up period. • SAEs, MAAEs, AEs leading to withdrawal, AESIs from Day 1 to EoS.
Secondary	
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.	• Omicron BA.4/5 and ancestral SARS-CoV-2 D614G GMTs at all planned timepoints (Days 91, 181, 365). • SRR[a,b] against Omicron BA.4/5 and ancestral SARS-CoV-2 D614G at all planned timepoints.
To assess the incidence of SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).	• 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.[c]
Exploratory	
To characterize the antibody response against emerging variants.	GMTs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.

Objectives	Endpoints
To characterize SARS-CoV-2 isolates.	Characterize the SARS-CoV-2 genomic sequence of viral isolates.
To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19.	Immune response markers.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; EoS = end of study; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PRC = reverse transcriptase polymerase chain reaction; rVE = relative vaccine efficacy; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

a. 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.

b. 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.

c. SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody 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.

Part 2

Objectives	Endpoints
Primary	
To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.	rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent the first event of COVID-19 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 on a respiratory sample. • 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

Objectives	Endpoints
	breathing, OR clinical or radiographical evidence of pneumonia; AND – ≥1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
To evaluate the safety and reactogenicity of 10 µg mRNA-1283.815.	• Solicited local and systemic ARs during a 7-day follow-up period after the study injection for adolescents and previously unvaccinated participants. • Unsolicited AEs during the 28-day follow-up period after study injection (all participants). • SAEs, MAAEs, AEs leading to withdrawal, AESIs from Day 1 to EoS (all participants).
Secondary	
To assess the incidence of severe COVID-19 (mRNA-1283.815 and mRNA-1273.815).	Severe COVID-19 is defined as virologically confirmed SARS-CoV-2 infection with ANY of the following starting 14 days after study injection: • Clinical signs at rest indicative of severe systemic illness: respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300 mmHg; OR • Respiratory failure or acute respiratory distress syndrome (requiring high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic BP <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); OR • Significant acute renal, hepatic, or neurologic dysfunction; OR • Admission to an intensive care unit or death.
To assess the incidence of SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).	• 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.[a]

Objectives	Endpoints
Exploratory	
To characterize the antibody response against emerging variants.	GMTs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.
To characterize SARS-CoV-2 isolates.	Characterize the SARS-CoV-2 genomic sequence of viral isolates.
To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19.	Immune response markers.
To characterize the neutralizing antibody response against Omicron XBB.1.5 (1283.815 and 1273.815) at all planned timepoints.	• Omicron XBB.1.5 GMTs at all planned timepoints • SRR[b,c] against Omicron XBB.1.5 at all planned timepoints.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BP = blood pressure; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; EoS = end of study; FiO2 = fraction of inspired oxygen; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; PaO_2 = the oxygen pressure in arterial blood; rVE = relative vaccine efficacy; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = pulse oximetry; SSR = seroresponse rate.

a. SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody 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.

b. 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.

c. 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.

Overall Design Synopsis:

This is a Phase 3 randomized, observer-blind, active-controlled, multicenter, 2-stage, group-sequential study. The study will evaluate the immunogenicity, reactogenicity and safety of mRNA-1283.222 in Part 1 and of mRNA-1283.815 in Part 2. The rVE (mRNA-1283 vs mRNA-1273) from Part 1 and Part 2 combined will be assessed.

Up to approximately 33,574 participants ≥12 years of age who are medically stable will be randomized in a 1:1 ratio to mRNA-1273 or mRNA-1283 (variant formulations) in Part 1 and Part 2. In Part 1, approximately 11,500 participants completed enrollment with mRNA-1283.222 or mRNA-1273.222. In Part 2, up to approximately 22,074 participants will be randomized to mRNA-1283.815 or mRNA-1273.815.

The study randomization will use age as a stratification factor (12 to <18, 18 to <65, and ≥65 years of age) for Part 1 and Part 2. Approximately 2000 (~1000 each in Part 1 and Part 2) adolescents (12 to <18 years) and approximately 30% of participants ≥65 years of age will be

enrolled (Part 1 and Part 2 combined). In Part 2, previous COVID-19 vaccination status (Yes/No) will be a stratification factor.

Study Arm and Dose Level in Part 1 and Part 2

Part 1			
Treatment Group	**Vaccination Received**	**Total Dose**	**N (total)**
1	mRNA-1283.222	10 µg	Approximately 5750
2	mRNA-1273.222	50 µg	Approximately 5750
Part 2			
1	mRNA-1283.815	10 µg	Up to ~11,037
2	mRNA-1273.815	50 µg	Up to ~11,037

All participants in Part 1 were to have previously received a primary series of an authorized/approved COVID-19 vaccine and those aged ≥18 years were to also have received at least 1 booster dose. Participants 12 to <18 years have no requirement to have received a booster prior to entry. In Part 2, 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. In Part 1, 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 polymerase chain reaction (PCR) within 90 days prior to enrollment were excluded as well.

Except for appropriately delegated unblinded pharmacists, vaccine administrators and monitors, all personnel involved in the conduct of the trial will remain blinded to individual treatment assignment until study unblinding. Study visits will consist of a Screening Visit, Vaccination Visit at Day 1 and subsequent in-person study visits 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 each part of the study. Illness visits for potential symptoms of COVID-19 will include a nasal swab for PCR testing.

A Data Safety Monitoring Board will monitor the study for any safety concerns and review interim rVE data as needed.

Number of Participants:

In total, up to approximately 33,574 participants ≥12 years of age who are medically stable will be randomized. In Part 1, approximately 11,500 participants will be enrolled. In Part 2, up to approximately 22,074 participants will be enrolled.

Study Arms and Duration:

Participants in Part 1 and Part 2 will be randomized in a 1:1 ratio to mRNA-1283 or mRNA-1273 (variant formulations). In Part 1, participants received mRNA-1283.222 or mRNA-1273.222. In Part 2, participants will receive mRNA-1283.815 or mRNA-1273.815.

Total duration for each participant is 12 months. Participants will receive one IM injection of study intervention.

Statistical Considerations

Part 1

Primary Hypotheses for the 4 co-primary immunogenicity endpoints:

1. The null hypothesis H^1_0: Antibody geometric mean titer (GMT) 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 GMT of mRNA-1283.222 at Day 29 over the GMT of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).
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%.
3. The null hypothesis H^3_0: Antibody GMT 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 GMT of mRNA-1283.222 at Day 29 over the GMT of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).
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 study would meet the primary immunogenicity objectives if non-inferiority is demonstrated in the 4 co-primary immunogenicity endpoints.

Part 1, Part 2

The rVE objective will be demonstrated with Part 1 and Part 2 combined data.

Primary Hypothesis for rVE:

1. The null hypothesis H_0: rVE of mRNA-1283 as compared to mRNA-1273 (variant formulation) is inferior to prevent the first occurrence of COVID-19. The prespecified non-inferiority margin is 10%.

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 vaccine injection, and the null hypothesis is: H_0: rVE $\leq$-10% (this is equivalent to hazard ratio (HR) $\geq$1.1, where rVE = 1-HR).

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1283 and mRNA-1273 (variant formulation) at a 2-sided alpha-adjusted significance level, using the per protocol set for efficacy (PPSE).

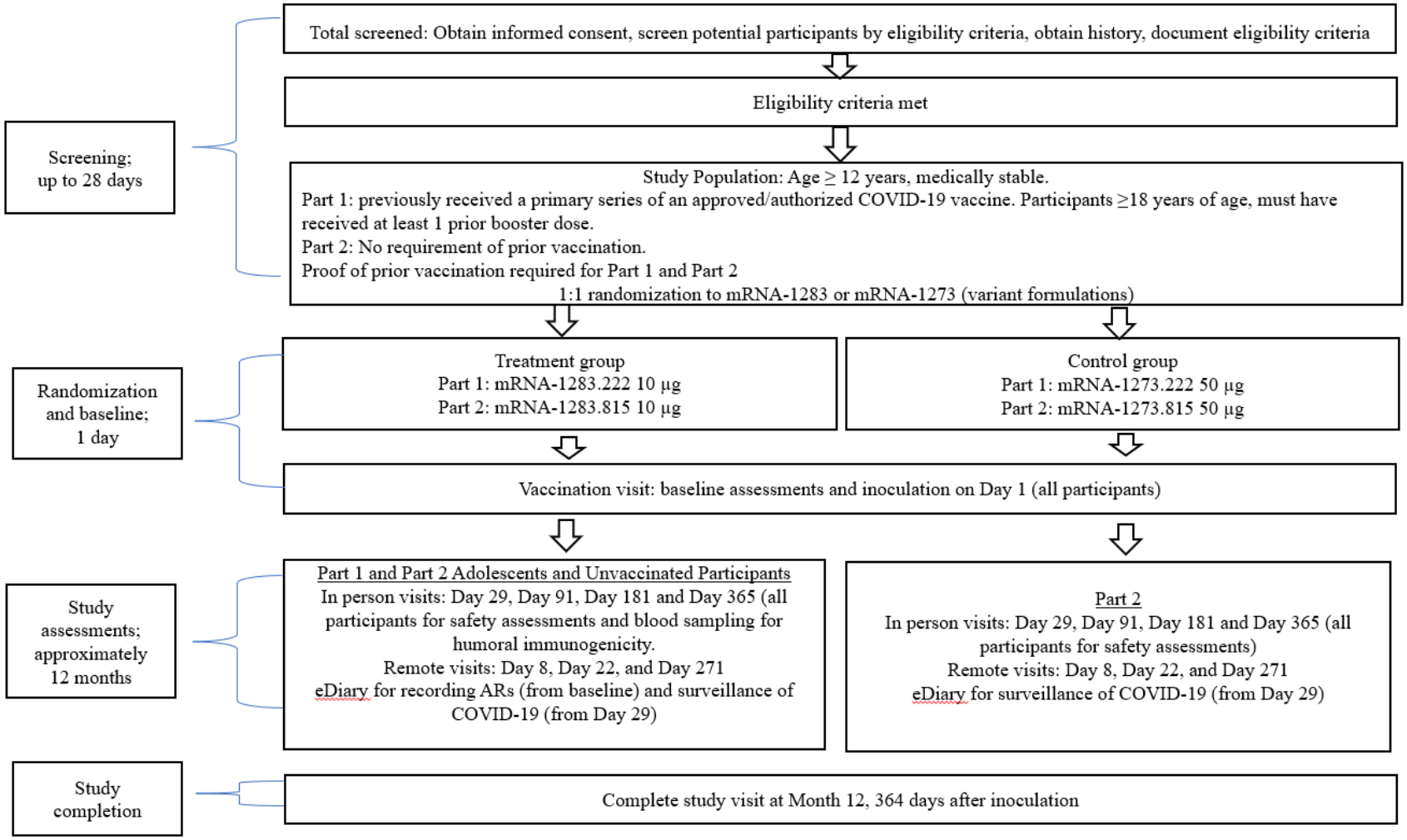
Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, and AEs leading to discontinuation.

The number and percentage of participants with any solicited local or systemic AR and any solicited AR during the 7-day follow-up period after study injection by toxicity grade will be assessed. The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will also be summarized.

1.2. Study Schema

A study schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: AR = adverse reaction; COVID-19 = coronavirus disease 2019; eDiary = electronic diary; mRNA = messenger ribonucleic acid.

1.3. Schedule of Assessments

Table 1: Schedule of Assessments

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Type of Visit	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**SC**	**C**		
Month					**M1**	**M3**	**M6**	**M9**	**M12**		
Study Visit Day	**Screening[a]**	**D1**	**D8**	**D22**	**D29**	**D91**	**D181**	**D271**	**D365/ EoS**	**Unscheduled Visit[b]**	**Illness Visit[b]**
Window Allowance (D)	-28	-3	+3	+3	-3/+7	±7	±14	±7	±14	N/A	N/A
Days Since Vaccination	-	0	7	21	28	90	180	270	364		
ICF, demographics, concomitant medications, medical history[c]	X										
Confirm participant meets inclusion and exclusion criteria	X	X									
Physical examination[d]	X	X			X	X	X		X	X	X
Vital signs[e]	X	X								X	X
Pregnancy testing[f]	X	X									
Randomization		X									

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Type of Visit	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**SC**	**C**		
Month					**M1**	**M3**	**M6**	**M9**	**M12**		
Study Visit Day	**Screening[a]**	**D1**	**D8**	**D22**	**D29**	**D91**	**D181**	**D271**	**D365/ EoS**	**Unscheduled Visit[b]**	**Illness Visit[b]**
Window Allowance (D)	-28	-3	+3	+3	-3/+7	±7	±14	±7	±14	N/A	N/A
Days Since Vaccination	-	0	7	21	28	90	180	270	364		
Dosing											
Study injection (including 15-minute postdosing observation period)		X									
Surveillance for COVID-19											
Nasal swab for PCR testing[g]		X			X	X	X		X	X	X[h]
Blood for SARS-CoV-2 surveillance		X			X	X	X		X	X	
eDiary prompts for COVID-19 and major changes in health					eDiary prompts every 2 weeks starting at Day 29 through Day 365/EoS (±1 day)						
Immunogenicity Assessment											
Blood for humoral immunogenicity[i]		X			X	X	X		X	X	

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Type of Visit	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**SC**	**C**		
Month					**M1**	**M3**	**M6**	**M9**	**M12**		
Study Visit Day	**Screening[a]**	**D1**	**D8**	**D22**	**D29**	**D91**	**D181**	**D271**	**D365/ EoS**	**Unscheduled Visit[b]**	**Illness Visit[b]**
Window Allowance (D)	-28	-3	+3	+3	-3/+7	±7	±14	±7	±14	N/A	N/A
Days Since Vaccination	-	0	7	21	28	90	180	270	364		
Reactogenicity Assessments – Part 1: All Participants and Part 2: Adolescents and Previously Unvaccinated Only											
eDiary activation for recording solicited AR (7 days)[j]		X									
Review of eDiary			X								
Safety Assessments											
Safety phone calls			X	X				X			
Recording of unsolicited AEs		X	X	X	X						

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Type of Visit	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**SC**	**C**		
Month					**M1**	**M3**	**M6**	**M9**	**M12**		
Study Visit Day	**Screening[a]**	**D1**	**D8**	**D22**	**D29**	**D91**	**D181**	**D271**	**D365/ EoS**	**Unscheduled Visit[b]**	**Illness Visit[b]**
Window Allowance (D)	-28	-3	+3	+3	-3/+7	±7	±14	±7	±14	N/A	N/A
Days Since Vaccination	-	0	7	21	28	90	180	270	364		
Recording of MAAEs, AESIs, AE leading to withdrawal and concomitant medications relevant to or for the treatment of these events[k]		X	X	X	X	X	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[k]	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations		X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; COVID-19 = coronavirus disease 2019; C=clinic; D = day; eDiary = electronic diary; EoS = end of study; ICF = informed consent form; M=month; MAAE = medically attended adverse event; N/A = not applicable, PCR=polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SoA=schedule of assessments.

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

a. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window. Testing at Baseline can be performed up to 3 days before Day 1.

b. An unscheduled visit is scheduled when a participant withdraws early from the study, missed a visit for any reasons other than illness, or for any other non-safety reason. An illness visit may be prompted by reactogenicity, COVID-19 illness, or new or ongoing AEs. A nasal swab for PCR testing is to be obtained for an illness visit. Clinical information will also be collected to evaluate signs and symptoms.

c. Verbal medical history is acceptable.

d. Physical examination: a full physical examination, including vital signs, height, and weight, will be performed at Screening and Day 1. BMI will be calculated at the Screening Visit only. Symptom-directed physical examinations will be performed on Day 29, Day 91, Day 181, Day 365/EoS, and during unscheduled or illness visits. On the day of the vaccination, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as an MAAE.

e. Vital sign measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of injection, vital signs will be collected once before the injection and once 15 minutes after injection. When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥38.0°C/100.4°F) before dosing must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator. Vital signs may be collected at other in-person visits in conjunction with a symptom-directed physical examination. A pulse oximeter measurement may be performed at unscheduled or illness visits, if applicable/available.

f. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the injection on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's FSH level should be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.

g. Nasal swabs are to be collected at routine clinic visits as shown in the SoA. If not collected at a routine visit, an unscheduled visit should be performed for a nasal swab sample. In addition to the nasal swab sample shown in the SoA, a nasal swab sample will be collected if signs and symptoms are suggestive of COVID-19. If a participant experiences symptoms suggestive of COVID-19, the participant should be directed, as soon as possible and within 72 hours, to have a nasal swab sample taken for PCR testing. This sample should be sent to the central lab within 24 hours. If a rapid antigen test was used for screening at home, participants will still be required to present to the study site for SARS-CoV-2 PCR testing as soon as possible and within 72 hours.

h. **Part 1 Only:** An additional nasal swab will be collected to test for the presence of other respiratory pathogens.

i. Samples for humoral immunogenicity must be collected prior to receipt of vaccination on Day 1. All participants will have blood drawn for humoral immunogenicity.

j. **Part 1: All Participants and Part 2: Adolescents and Previously Unvaccinated Participants Only:** The participant will record data in the eDiary approximately 15 minutes after dosing while at the study site, with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of dosing, and for 6 days following. Any solicited AR that is ongoing beyond Day 7 will be reported verbally by participants at the scheduled remote visits, until resolution. Participants will be given thermometers to record their body temperatures and rulers to measure any injection site reactions.

k. Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations.

2. INTRODUCTION

2.1. Study Rationale

SARS-CoV-2 variants have emerged and are likely to continue to emerge and some variants have the potential to circumvent immunity associated with previous infection or vaccination. Variants of concern, as defined by the WHO (WHO 2021), are associated with increased infectivity and a reduction in the ability of convalescent sera or sera from vaccinated individuals to neutralize these emergent variants. Mutations occurring in the RBD and the NTD of the S protein are of particular concern, as this site includes the dominant neutralization epitopes on the S protein, and these mutations could impact the ability of antibodies elicited by infection or vaccination in neutralizing the virus (Greaney et al 2021).

To address the need for updated vaccination strategies, the Sponsor has used its mRNA-based platform to develop a custom SARS-CoV-2 mRNA vaccine candidate, mRNA-1283, which encodes for the NTD and RBD of the S protein of SARS-CoV-2. The mRNA-1283 design enables longer shelf-life at refrigerated temperatures while providing a safe and tolerable vaccine with potent immune responses at lower doses compared to the original vaccine mRNA-1273. In the polypeptide encoded by mRNA-1283, the NTD and RBD sequences are linked together with a 7-amino-acid flexible linker. The linked NTD-RBD polypeptide is attached via a 5-amino-acid flexible linker to a 23-amino-acid hemagglutinin transmembrane domain from influenza, which is intended to anchor the linked NTD-RBD polypeptide into the cell membrane of antigen-expressing cells. Potent nAbs to the RBD and NTD of SARS-CoV-2 have been described in the literature (Brouwer et al 2020, Liu et al 2020, Lv et al 2020) and support the design of candidate vaccines. Animal challenge and protection studies have demonstrated protective responses elicited by RBD-based vaccines (Chen et al 2020, Yang et al 2020).

The Sponsor has previously evaluated mRNA-1283 and mRNA-1283.211 (contains equal mRNA amounts of the ancestral SARS-CoV-2 and Beta variant RBD and NTD) in a Phase 1 (mRNA-1283-P101) and Phase 2a (mRNA-1283-P201) study. In study P101, mRNA-1283 was administered as a 2-dose primary series (10, 30, 100 µg) in approximately 80 participants. mRNA-1283 was well tolerated as a primary series and elicited a similar or numerically higher nAb response against the ancestral SARS-CoV-2 D614G compared to an mRNA-1273 100 µg primary series comparator group, 28 days after completion of the primary series. In study P201, mRNA-1283 and mRNA-1283.211 were administered as a first booster dose (2.5, 5 and 10 µg) after immunization with the mRNA-1273 primary series in approximately 350 participants. The safety and reactogenicity profile of mRNA-1283 and mRNA-1283.211 were overall similar to a within-study 50 µg mRNA-1273 comparator. The immunogenicity results indicated that mRNA-1283 and mRNA-1283.211 elicited similar or numerically higher nAb responses against the ancestral SARS-CoV-2 (D614G) and Beta (B.1.351) variants 28 days after the mRNA-1283 and mRNA-1283.211 booster doses.

Based on the previous evaluation of mRNA-1283 and mRNA-1283.211, the Sponsor has selected the 10-µg booster dose for the mRNA-1283.222 bivalent vaccine (contains equal amount of the ancestral SARS-CoV-2 and Omicron BA.4/5 variant) as a dose with a favorable safety and reactogenicity profile, similar to the 50-µg booster dose of mRNA-1273 booster vaccine. Additionally, 10 µg of mRNA-1283 (including 10 µg of the bivalent vaccine

Beta-containing mRNA-1283.211) elicited potent nAb responses against the ancestral SARS-CoV-2 D614G and the Beta variant (the variant contained in the vaccine) in the P201 study, 28 days after the booster dose.

The purpose of this study is to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1283.222 in Part 1 and of mRNA-1283.815 in Part 2. The rVE from Part 1 and Part 2 combined will be assessed.

2.2. Background

The Sponsor has developed a rapid-response, proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently.

2.2.1. mRNA-1283

The Sponsor is using its mRNA-based platform to develop mRNA-1283, a custom LNP-encapsulated, mRNA-based SARS-CoV-2 vaccine candidate that has improved shelf-life at refrigerated temperatures and preliminary data suggest that it has a similar immunogenicity and reactogenicity profile to mRNA-1273 at a lower dose level compared to mRNA-1273.

2.2.2. mRNA-1283.222

The bivalent vaccine candidate, mRNA-1283.222, contains equal amounts of 2 mRNAs; one mRNA encodes for the RBD and NTD of the S protein of the ancestral SARS-CoV-2, and the other mRNA encodes for the RBD and NTD of the S protein of Omicron BA.4/5 variants. The S protein sequence is identical for the BA.4 and BA.5 sublineages.

2.2.3. mRNA-1273.222

The approved bivalent vaccine, mRNA-1273.222, contains 2 mRNAs encoding for the entire S proteins of the ancestral SARS-CoV-2 and Omicron BA.4/5 variants.

2.2.4. mRNA-1283.815

A monovalent vaccine candidate composed of the mRNA-LNP encoding the linked NTD-RBD of the S protein of the XBB.1.5 variant. The mRNA is formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG.

2.2.5. mRNA-1273.815

The approved monovalent vaccine composed of the mRNA-LNP encoding the S protein of the XBB.1.5 variant. The mRNA is formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG.

2.2.6. Nonclinical Studies

Previous nonclinical studies in Balb/c mice have been performed to evaluate dose ranging responses to mRNA-1283 (immunogenicity) versus mRNA-1273. These nonclinical studies in mice assessed immunogenicity by evaluating bAb and nAb responses as well as Th1-directed CD4+ and CD8+ responses elicited by mRNA-1283. mRNA-1283 was shown to be immunogenic in Balb/c mice, indicating a potent bAb response and neutralization activity.

In mice immunized with mRNA-1283, potent, Th1-dominant, CD4+ response (production of interferon-γ, interleukin-2, tumor necrosis factor-α), as well as CD8+ T cell responses to spike peptide pools, was observed. Preclinical evaluations have also been performed to evaluate mRNA-1283 as boosters in animals previously vaccinated with a 2-dose primary series of mRNA-1273 or mRNA-1283. All boosters significantly increase bAb and nAb titers. Challenge studies in mice were also conducted to evaluate protection by mRNA-1283. Mice receiving a primary series vaccination with mRNA-1283 were protected against challenge by SARS-COV-2 BA.1 strain. In addition to mRNA-1283 which encodes NTD and RBD from the ancestral strain, preclinical evaluation of mRNA-1283 vaccines adapted to match circulating variants has also been performed in mice. This includes bivalent formulations such as mRNA-1283.211 (a 1:1 mix of mRNAs encoding NTD and RBD from S of ancestral SARS-CoV-2 and Beta variants) and mRNA-1283.222 (a 1:1 mix of mRNAs encoding NTD and RBD from S of ancestral SARS-COV-2 and Omicron BA.4/BA.5 variants). Variant matched vaccines elicited higher bAb and nAb titers against the specific variants with bivalent formulations eliciting the highest breadth of response against multiple variants. Monovalent SARS-COV-2 XBB variant containing mRNA-1283 vaccines have also been evaluated preclinically in both primary series and booster studies. mRNA-1283.815 (containing NTD and RBD from XBB.1.5 strain) or mRNA-1283.116 (containing NTD and RBD from XBB.1.16 strain) were comparably effective in eliciting high nAb titers against these XBB strains that were comparable or higher than mRNA-1273 groups.

2.2.7. Clinical Studies

The mRNA-1283-P101 Phase 1 (NCT04813796) and mRNA-1283-P201 Phase 2a (NCT05137236) trials are ongoing. In Study P101, mRNA-1283 was administered as a 2-dose primary series in different dose levels. At Day 57, participants were randomized to each dose of mRNA-1283 (10 µg, 30 µg, 100 µg), placebo, and mRNA-1273 (100 µg). mRNA-1283 was well tolerated and the ARs and TEAEs were similar between the mRNA-1283 and mRNA-1273 treatment groups. The primary series elicited a similar or numerically higher nAb response against the ancestral SARS-CoV-2 D614G (0.9x-1.4x) compared to an mRNA-1273 100 µg primary series comparator group, 28 days after completion of the primary series.

An interim analysis of the Phase 2a mRNA-1283-P201 (Day 29) trial evaluated mRNA-1283 (2.5 µg, 5 µg, 10 ug), mRNA-1283.211 (5 µg, 10 µg) and mRNA-1273 (50 µg) as a first booster dose, after immunization with the mRNA-1273 100 µg primary series. The safety and reactogenicity profiles of mRNA-1283 and mRNA-1283.11 were overall similar to a within-study mRNA-1273 50-µg comparator group. Additionally, the P201 immunogenicity results indicated that mRNA-1283 and mRNA-1283.211 elicited similar or numerically higher (1x to 2x) nAb responses against the ancestral SARS-CoV-2 (D614G) and Beta (B.1.351) variants 28 days after the mRNA-1283 and mRNA-1283.211 booster doses.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of study intervention may be found in the IB.

2.3.1. Risk Assessment

Safety will be monitored throughout the study (Table 1) and by a DSMB (Section 10.1.6.1).

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precautionary measure, all participants will remain under observation at the study site for at least 15 minutes after vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection, and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

IM vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. Local ARs can typically include pain, erythema (redness), or swelling (hardness) at the injection site, which usually occur within 24 hours of vaccination.

Most systemic AEs observed after vaccination do not exceed mild-to-moderate severity and these can include (but are not limited to) fatigue, headache, and myalgia.

Laboratory abnormalities (including increases in liver functional tests and serum lipase levels) following vaccination have been observed in clinical studies with mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and lab values returned toward baseline (Day 1) values. Further details are provided in the current IB. Safety testing for laboratory abnormalities will not be performed on a routine basis.

In the post-authorization setting, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of cases have been reported in adolescent males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Investigators and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (see Section 10.5).

An interim analysis of the Phase 1 and Phase 2a studies (Day 57 and Day 29, respectively) indicated that the safety profile of mRNA-1283 (including mRNA-1283.222) is generally similar to mRNA-1273.

In the Phase 2 study (mRNA-1283-P201) the highest reported frequencies of any solicited ARs within 7 days after injection occurred in participants who received mRNA-1273 50 µg (88.9%) and mRNA-1283 10 µg (88.5%). Pain was the most commonly reported solicited local AR within 7 days after injection with the highest incidence reported in the mRNA-1273 50-µg group (83.3%) compared to 55.6% to 68.0% in the mRNA-1283 groups and 58.7% to 65.2% in the mRNA-1283.211 groups. The incidence of axillary swelling or tenderness within 7 days after injection was higher in the mRNA-1283 5-µg (25.9%) and mRNA-1283 10-µg (23.5%) groups compared to mRNA-1283.211 (14.9% to 18.6%) and mRNA-1273 (12.5%) groups. Fatigue,

nausea/vomiting, arthralgia, and myalgia were reported by a higher proportion of participants in the mRNA-1273 group (58.8%, 29.2%, 40.0%, and 56.0%, respectively) than the mRNA-1283 and mRNA-1283.11 groups (43.1% to 51.0%, 4.7% to 15.2%, 23.3% to 34.8%, and 29.4% to 38.0%, respectively).

There were no Grade 4 or fatal TEAEs within 28 days after injection.

2.3.2. Benefit Assessment

The mRNA-1283 vaccine candidate elicits a potent immune response against SARS-CoV-2 and VOCs (Section 2.2.7), and it was designed with the objective of providing a longer shelf-life at refrigerated temperatures while having a safe and tolerable vaccine that can elicit immune responses which are comparable to the original vaccine, mRNA-1273, and at lower doses compared to mRNA-1273. mRNA-1283 has been shown to elicit potent nAb responses against the ancestral SARS-CoV-2 D614G and the Beta variant in the mRNA-1283-P201 study. Specifically, mRNA-1283 and mRNA-1283.211 were administered as a first booster dose (2.5, 5, and 10 µg) after immunization with the mRNA-1273 primary series in approximately 350 participants. The safety and reactogenicity profile of mRNA-1283 and mRNA-1283.211 were overall similar to a within-study mRNA-1273 50-µg comparator. The immunogenicity results indicated that mRNA-1283 and mRNA-1283.211 elicited similar or numerically higher nAb responses against the ancestral SARS-CoV-2 (D614G) and Beta (B.1.351) variants 28 days after the mRNA-1283 and mRNA-1283.211 booster doses.

Participants in this study will be evaluated and monitored for SARS-CoV-2 infection at baseline (Day 1) until the end of the study and will be contributing to the development of a vaccine against COVID-19.

2.3.3. Overall Benefit/Risk Conclusion

The evolving antigenic variation of SARS-CoV-2 underscores the urgent need for vaccination strategies that induce broad and durable protection against COVID-19, specifically against VOCs with attendant risk of viral escape. The Sponsor is developing the next generation SARS-CoV-2 mRNA vaccine candidate that may improve product stability compared to mRNA-1273 and therefore vaccine deployment globally.

Based on the safety and immunogenicity clinical data available for mRNA-1283, the Sponsor considers the potential benefits of participation in this study to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives to be evaluated in this study and endpoints associated with each objective are provided in Table 2 for Part 1 and Table 3 for Part 2.

Table 2: Part 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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.	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[a] 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[a] difference of ancestral SARS-CoV-2 D641G between mRNA-1283.222 10 µg and mRNA-1273.222 50 µg at Day 29.
To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.	rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent the first event of COVID-19 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 on a respiratory sample. • 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

Objectives	Endpoints
	– ≥1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
To evaluate the safety and reactogenicity of 10 µg mRNA-1283.222.	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period. • Unsolicited AEs during the 28-day follow-up period. • SAEs, MAAEs, AEs leading to withdrawal, AESIs from Day 1 to EoS
Secondary	
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.	• Omicron BA.4/5 and ancestral SARS-CoV-2 D614G GMTs at all planned timepoints (Days 91, 181, 365). • SRR[a,b] against Omicron BA.4/5 and ancestral SARS-CoV-2 D614G at all planned timepoints.
To assess the incidence of SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).	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.[c]
Exploratory	
To characterize the antibody response against emerging variants.	GMTs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.
To characterize SARS-CoV-2 isolates.	Characterize the SARS-CoV-2 genomic sequence of viral isolates.
To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19.	Immune response markers

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; EoS = end of study; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR= reverse transcriptase polymerase chain reaction; rVE = relative vaccine efficacy; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = pulse oximetry; SSR = seroresponse rate.

a. 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.

b. 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.

c. SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody 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.

Table 3: Part 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.	rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent the first event of COVID-19 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 on a respiratory sample. • 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 for SARS-CoV-2 by RT-PCR.
To evaluate the safety and reactogenicity of 10 µg mRNA-1283.815.	• Solicited local and systemic ARs during a 7-day follow-up period after the study injection for adolescents and previously unvaccinated participants. • Unsolicited AEs during the 28-day follow-up period after study injection (all participants). • SAEs, MAAEs, AEs leading to withdrawal, AESIs from Day 1 to EoS (all participants).

Objectives	Endpoints
Secondary	
To assess the incidence of severe COVID-19 (mRNA-1283.815 and mRNA-1273.815).	Severe COVID-19 is defined as virologically confirmed SARS-CoV-2 infection with ANY of the following starting 14 days after study injection: • Clinical signs at rest indicative of severe systemic illness: respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300 mmHg; OR • Respiratory failure or acute respiratory distress syndrome (requiring high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic BP <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); OR • Significant acute renal, hepatic, or neurologic dysfunction; OR • Admission to an intensive care unit or death.
To assess the incidence of SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).	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.[a]
Exploratory	
To characterize the antibody response against emerging variants.	GMTs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.
To characterize SARS-CoV-2 isolates.	Characterize the SARS-CoV-2 genomic sequence of viral isolates.
To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19.	Immune response markers.
To characterize the neutralizing antibody response against Omicron XBB.1.5 (1283.815 and 1273.815) at all planned timepoints.	Omicron XBB.1.5 GMTs at all planned timepoints. SRR[b,c] against Omicron XBB.1.5 at all planned timepoints.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BP = blood pressure; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; EoS = end of study; FiO2 = fraction of inspired oxygen; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal;

RT-PCR= reverse transcriptase polymerase chain reaction; PaO_2 = the oxygen pressure in arterial blood; rVE = relative vaccine efficacy; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = pulse oximetry; SSR = seroresponse rate.

a. SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody 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.

b 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.

c. 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.

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 will evaluate the immunogenicity, reactogenicity, and safety of mRNA-1283.222 in Part 1 and of mRNA-1283.815 in Part 2. The rVE from Part 1 and Part 2 combined will be assessed.

Up to approximately 33,574 participants ≥12 years of age who are medically stable will be randomized in a 1:1 ratio to mRNA-1273 or mRNA-1283 (variant formulations) in Part 1 and Part 2. In Part 1, approximately 11,500 participants completed enrollment with mRNA-1283.222 or mRNA-1273.222. In Part 2, up to approximately 22,074 participants will be randomized to mRNA-1283.815 or mRNA-1273.815.

The study randomization will use age as a stratification factor (12 to <18, 18 to <65, and ≥65 years of age) for Part 1 and Part 2. Approximately 2000 (~1000 each in Part 1 and Part 2) adolescents (12 to <18 years) and approximately 30% of participants ≥65 years of age will be enrolled (Part 1 and Part 2 combined). In Part 2, previous COVID-19 vaccination status (Yes/No) will be a stratification factor. Sample size determination is outlined in Section 9.3. The potential number of participants in treatment group is described in Table 4.

Table 4: Study Arm and Dose Level in Part 1 and Part 2

Treatment Group	Vaccination Received		Total Dose	Approximate N (total)	
	Part 1	Part 2		Part 1	Part 2
1	mRNA-1283.222	mRNA-1283.815	10 µg	~5750	Up to ~11,037
2	mRNA-1273.222	mRNA-1273.815	50 µg	~5750	Up to ~11,037

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

In Part 1, 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 2, 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 are to be excluded.

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 each part of the study. Illness visits for potential symptoms of COVID-19 will include nasal swab for PCR testing.

Table 1 displays the SoA for Part 1 and Part 2.

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 (refer to Section 6.4).

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.

In Part 1, an interim analysis of safety and immunogenicity will be performed after all participants have been followed for at least 29 days after the booster dose (Section 9.8.1).

4.2. Scientific Rationale for Study Design

mRNA-1283 was designed to provide a safe and tolerable vaccine with longer shelf-life at refrigerated temperatures than the Sponsor's original mRNA vaccine, mRNA-1273, with at least similar immunogenicity and efficacy to mRNA-1273 at a lower dose level. Part 1 was designed to evaluate the safety (including reactogenicity) and non-inferior antibody responses of mRNA-1283.222 compared to mRNA-1273.222. A pooled analysis with Part 1 and Part 2 data will support the rVE objective of mRNA-1283 compared to mRNA-1273 (variant formulations) with a 10% non-inferiority margin.

Because it is possible that participants are exposed to SARS-CoV-2 through community exposure, nasal swab samples and samples for humoral immunogenicity will be collected before vaccination on Day 1 to differentiate between natural infection and vaccine-induced antibody responses. Subsequent nasal swabs should be collected at the visit dates in the SoA. Furthermore, nasal swab specimen(s) for assessment of SARS-CoV-2 will also be collected at any time during the study period if participants have symptoms suggestive of COVID-19, at the investigator's discretion. Additionally, clinical information will be collected to evaluate the severity of the clinical case. Part 2 will also evaluate severe COVID-19.

4.3. Justification for Dose

Based on the previous evaluation of mRNA-1283 and mRNA-1283.211, the 10-µg booster dose for the mRNA-1283.222 bivalent vaccine (contains equal amount of the ancestral SARS-CoV-2 and Omicron BA.4/5 variant) was selected as the dose with a favorable safety and reactogenicity profile, similar to the 50-µg booster dose of mRNA-1273 booster vaccine. Additionally, 10 µg of mRNA-1283 (including 10 µg of the bivalent Beta-containing mRNA-1283.211) elicited potent nAb responses against the ancestral SARS-CoV-2 D614G and the Beta variant (the variant contained in the vaccine) in the mRNA-1283-P201 study 28 days after the booster dose, which were numerically similar to or higher than those after the 50-µg booster dose of mRNA-1273. In Part 1, the 10 µg of the Omicron BA.4/5 containing mRNA-1283.222 vaccine in comparison to the mRNA-1273.222 50-µg vaccine was evaluated. In Part 2, the 2023/2024 COVID-19 variant

containing vaccines, Omicron XBB.1.5-containing products (mRNA-1283.815 or mRNA-1273.815) will be used.

4.4. End of Study Definition

For the Sponsor, the EoS is defined as the date that the analyses are completed for the primary and secondary endpoints for the study.

A participant is considered to have completed the study if the participant has completed the EoS visit.

5. STUDY POPULATION

The prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply during the screening period and at Day 1, unless noted otherwise:

Age

1. Male or female, at least 12 years of age at the time of consent (Screening Visit).

Type of Participant and Disease Characteristics

2. Investigator's assessment that the participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.

Sex and Contraceptive/Barrier Requirements

3. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized. An FSH level should be measured at the discretion of the investigator to confirm postmenopausal status, if necessary.
4. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
   - Has a negative pregnancy test at the Screening Visit and on the day of vaccination prior to vaccine dose being administered on Day 1.
   - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1). Adequate female contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label.
   - Has agreed to continue adequate contraception through 90 days following vaccine administration. See additional information on adequate contraception definition in Section 10.3.

Informed Consent

5. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.

Other Inclusion Criteria

6. Part 1: Has previously received a primary series of an authorized/approved COVID-19 vaccine. For participants ≥18 years of age, at least 1 booster dose must have also been received. Proof of prior vaccination is required. A heterologous vaccine regimen is acceptable.

   Part 2: No prior vaccination is required. For participants who have been previously vaccinated, proof of vaccination is required.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has had close contact, as defined by the CDC, with someone who had a SARS-CoV-2 infection in the past 14 days, or COVID-19 in the past 10 days. Participants may be rescreened after 14 days provided that they remain asymptomatic.
2. Participant is acutely ill or febrile (temperature ≥38.0°C/100.4°F) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window and will retain their initially assigned participant number.
3. Has tested positive for SARS-CoV-2 using an authorized/approved lateral flow/rapid antigen or PCR test within 90 days of Screening.
4. Has received a COVID-19 vaccine within 90 days of the Screening Visit.
5. Has history of myocarditis, pericarditis, or myopericarditis that has not fully resolved within 3 months prior to Screening.
6. Has received a total of 6 doses or more of COVID-19 vaccine.
7. Has received a COVID-19 vaccine at a dose different from the authorized/approved dose.
8. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
9. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease requiring immunosuppressive treatment or other immunosuppressive condition.
10. Dermatologic conditions that could affect local solicited AR assessments (eg, psoriasis patches affecting skin over the deltoid areas).
11. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any components of mRNA vaccine.
12. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
13. Any medical, psychiatric, or occupational condition, including reported history of substance abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
14. Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 181 days prior to Screening (for corticosteroids ≥10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.

15. Has received or plans to receive any licensed vaccine ≤60 days prior to the study injection (Day 1) or plans to receive a licensed vaccine within 60 days after the study injection.
16. Has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive during the study.
17. Diagnosis of malignancy within the previous 5 years (excluding nonmelanoma skin cancer).
18. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
19. Has participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
20. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Body temperature (oral) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the SoA (Section 1.3), or the participant may be discontinued from dosing at the discretion of the investigator (Section 7.1):

- Acute moderate or severe infection with or without fever at the time of dosing
- Fever, defined as body temperature ≥ 38.0°C/≥ 100.4°F at the time of dosing

Participants with a minor illness without fever, as assessed by the investigator, can be vaccinated.

Participants with a fever of ≥ 38.0°C/≥ 100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

The term "investigational product" refers to mRNA-1283 and mRNA-1273 (variant formulations) used in this study. In Part 1, mRNA-1283.222 and mRNA-1273.222 were administered. In Part 2, mRNA-1283.815 and mRNA-1273.815 will be used. The IP to be administered in this study is described in Table 5.

Table 5: Study Interventions Administered

Intervention	**mRNA-1283**	**mRNA-1273**
Intervention Name	mRNA-1283.222 (Part 1) mRNA-1283.815 (Part 2)	mRNA-1273.222 (Part 1) mRNA-1273.815 (Part 2)
Type	Vaccine	Vaccine
Dose Level	10 µg (mRNA)	50 µg (mRNA)
Route of Administration	IM injection	IM injection
Physical Description	Sterile liquid for injection, white-to-off-white dispersion.	Sterile liquid for injection, white-to-off-white dispersion.
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and Labeling	mRNA-1283.222 and mRNA-1283.815 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.	mRNA-1273.222 and mRNA-1273.815 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.

Abbreviations: AxMP = auxiliary medicinal product; IM = intramuscular; IMP = investigational medicinal product; mRNA = messenger ribonucleic acid; NIMP = non-investigational medicinal product.

mRNA-1283.222 contains 2 mRNAs, CX-025322 encoding for the linked NTD-RBD of the S protein of the ancestral SARS-CoV-2, and CX-035498 encoding for the linked NTD-RBD of the S protein of the Omicron subvariants BA.4 and BA.5. mRNA-1283.222 consists of each mRNA formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. The formulated mRNAs are combined in a 1:1 ratio. mRNA-1283.222 will be administered at a 10-µg dose level as an IM injection into the deltoid muscle or thigh on Day 1.

mRNA-1273.222 contains 2 mRNAs, CX-024414 encoding for the S-2P of Wuhan-Hu-1 and CX-034476 encoding for the S-2P of Omicron subvariants BA.4 and BA.5. mRNA-1273.222 consists of each mRNA formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. The formulated mRNAs are combined in a 1:1 ratio. mRNA-1273.222 will be administered at a 50-µg dose level as an IM injection into the deltoid muscle or thigh on Day 1.

mRNA-1283.815 is a monovalent vaccine composed of the mRNA-LNP encoding the linked NTD-RBD of the S protein of the XBB.1.5 variant. The mRNA is formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. mRNA-1283.815 will be administered at a 10-µg dose level as an IM injection into the deltoid muscle or thigh on Day 1.

mRNA-1273.815 is an approved monovalent vaccine composed of the mRNA-LNP encoding the S-2P of the XBB.1.5 variant. The mRNA is formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. mRNA-1273.815 will be administered at a 50-µg dose level as an IM injection into the deltoid muscle or thigh on Day 1.

Planned timepoints for immunogenicity assessments are provided in the SoA (Table 1).

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator and authorized site staff are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1. Clinical Study Material Preparation

The IP will be prepared for each participant based on their treatment group assignment.

The mRNA-1283.222 and mRNA-1283.815 injections will have a volume of 0.20 mL and will contain mRNA-1283.222 or mRNA-1283.815 at a dose of 10 µg.

The mRNA-1273.222 and mRNA-1273.815 injections will have a volume of 0.50 mL and will contain mRNA-1273.222 or mRNA-1273.815 at a dose of 50 µg.

IP preparation instructions are detailed in the Pharmacy Manual.

6.2.2. Clinical Study Material Administration

The IP will be administered as an IM injection into the deltoid muscle or thigh on Day 1. Preferably, the IP should be administered into the nondominant arm.

Participants will be monitored for a minimum of 15 minutes after administration of the study injection. Assessments will include vital sign measurements and monitoring for local or systemic reactions as shown in the SoA (Table 1).

The clinic will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either on-site resuscitation equipment and personnel or appropriate protocols for the rapid transport of a participant to a resuscitation area or facility are required.

Further instructions for the preparation, handling, and administration of IPs are described in the Pharmacy Manual.

6.2.3. Clinical Study Material Packaging and Labeling

All IPs used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, Code of Federal Regulations Title 21(CFR), Good Manufacturing Practice guidelines, ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

mRNA-1283.222 Product

Sterile mRNA-1283.222 injection contains 0.05 mg/mL of total RNA in an RNA-LNP dispersion in 20 mM Tris buffer containing 87 mg/mL sucrose and 1.1 mM acetate at pH 7.5. mRNA-1283.222 is packaged in 2R USP Type I borosilicate glass vials with PLASCAP vial seal containing a 13-mm FluroTec-coated plug stopper and has a 0.6-mL fill volume. mRNA-1283.222 will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

mRNA-1273.222 Product

Sterile mRNA-1273.222 is provided as a sterile solution for injection at a concentration of 0.1 mg/mL in 20 mM Tris buffer with sucrose, at pH 7.5 and presented in 2R USP Type I borosilicate glass vials with PLASCAP vial seal containing a 13-mm FluroTec-coated plug stopper with a 0.8-mL fill volume. mRNA-1273.222 will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

mRNA-1283.815 Product

Sterile mRNA-1283.815 injection contains 0.05 mg/mL of total RNA in an RNA-LNP dispersion in 20 mM Tris buffer containing sucrose and acetate, pH 7.5. mRNA-1283.815 is presented in 2R USP Type I borosilicate glass vials with a PLASCAP vial seal containing a 13-mm FluroTec-coated plug stopper and has a 0.6-mL fill volume. mRNA-1283.815 will have all required labeling per local regulations and will be supplied to the pharmacy in an unblinded manner.

mRNA-1273.815 Product

Sterile mRNA-1273.815 is provided as a sterile solution for injection at a concentration of 0.1 mg/mL in 20 mM Tris buffer containing sucrose and acetate, pH 7.5. mRNA-1273.815 is presented in 2R USP Type I borosilicate glass vials with an aluminum crimp seal containing a 13-mm FluroTec-coated plug stopper and has a 0.5-mL nominal fill volume. mRNA-1273.815 will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

6.2.4. Clinical Study Material Storage

The IP is stored in a secure area with limited access and must be protected from moisture and light until they are prepared for administration. The designated freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There should be an available backup freezer. The freezer should be connected to a backup generator. In addition, for IP accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IP that was not temperature controlled during shipment or storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods. Details about storage conditions of mRNA-1283 and mRNA-1273 are provided in the Pharmacy Manual.

6.2.5. Clinical Study Material Accountability

The investigator or designee must maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study treatment, and the return to the Sponsor or alternative disposition of used/unused product(s) in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. For further direction, refer to the Pharmacy Manual.

6.2.6. Clinical Study Material Handling and Disposal

The medical monitor or designee will reconcile the clinical study material in the interim and at the end of the study for compliance. Once fully reconciled at the site, the clinical study material can be destroyed at the investigational site or Sponsor-selected third party, as appropriate.

Study products may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be obtained and sent to the Sponsor or designee. For further direction refer to the Pharmacy Manual.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to the randomized study using an IRT. Before the study is initiated, directions for the IRT will be provided to each site. Participants will be randomized according to a 1:1 ratio to mRNA-1283.222 (10 μg) or mRNA-1273.222 (50 μg).

6.4. Blinding

This study is observer-blind as to treatment assignment. Dose preparation, administration and accountability will be performed by designated unblinded site personnel who will not participate in any of the clinical study evaluations. 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 laboratory personnel in charge of immunogenicity testing will be blinded to the treatment assignment of the samples tested throughout the course of the study.

The Sponsor will remain blinded to treatment assignment through the final efficacy analysis. For the safety and immunogenicity (Day 29) interim analysis in Part 1, a pre-identified Sponsor team will be unblinded to review group-level results. The DSMB may also review unblinded safety or

efficacy information at closed sessions (without the Sponsor's participation). Study sites will remain blinded.

Except in the case of medical necessity, a participant's treatment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the investigator will make every attempt to contact the CRO medical monitor to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblinding will be tracked via an audit trail in IRT and documented in the final study report.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of the dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Dose Modification

No dose modifications will be permitted.

6.7. Intervention After the End of the Study

There is no study intervention following the end of the study. Any AE occurring after the end of the study (Day 365) and considered to be caused by the study intervention must be reported to the Sponsor.

6.8. Treatment of Overdose

As the study intervention is to be administered by a healthcare provider, it is unlikely that an overdose will occur.

In the event of an overdose, the investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dose information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The following concomitant medication(s) and vaccine(s) must be recorded in the eCRF:

- All concomitant medications, except for vitamins and dietary supplements, administered from Screening through 28 days after the last dose (Day 29).
- Any non-study intervention administered during the period starting 30 days before the first dose of study intervention and ending at the last study visit (Day 365).
- Any concomitant medications and vaccines listed in Section 6.9.1.
- Any concomitant medications and vaccines relevant to an SAE or administered from the signing of the ICF through the last study visit for the treatment of an SAE.
- Any antipyretic or analgesic to treat or prevent fever or pain within 7 days post vaccination, including day of vaccination.
- Any concomitant medications and vaccines relevant to an MAAE administered from Day 1 through the last study visit.
- Prophylactic medications (ie, medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination) from Day 1 to 28 days after the last dose. For example, an antipyretic or analgesic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.

6.9.1. Prohibited Therapy

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PP analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥20 mg/day or the equivalent is not permitted. Inhaled and topical steroids are allowed.

- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- A vaccine not foreseen by the study protocol administered during the period from 60 days before through 60 days after each study vaccination.
- Immunoglobulins and/or any blood products administered during the study period.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.10.

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's request for any reason (or without providing any reason). A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. A participant who withdraws from the study will not be replaced.

At the time of discontinuing from the study, if possible, an unscheduled visit should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit foreseen in the protocol. All data collected until the date of withdrawal or last contact of the participant will be used for the analysis. A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Information relative to the withdrawal will be documented in EDC. The investigator will document whether the decision to withdraw a participant from the study was made by a participant, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE
- Death
- Lack of efficacy
- LTFU
- Noncompliance with study intervention
- Other
- Physician decision

- Pregnancy
- Progressive disease
- Protocol violation
- Recovery
- Screen failure
- Study terminated by Sponsor
- Technical problems
- Withdrawal by participant

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study because of an SAE or AE until resolution of the event.

7.3. Lost to Follow-up

If a participant does not complete a visit within the time window, every effort should be made to complete the assessments for that visit (even though outside of the defined visit window); the participant will continue with subsequent scheduled study visits per their original schedule (ie, relative to their Day 1 visit). If a participant still does not complete the visit after all these efforts, the visit will be classified as missed and all safety requirements of the missed visit will be captured and included in the subsequent visit.

A participant will be considered LTFU if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (when possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). All contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- A participant should be not considered LTFU until due diligence has been completed.

7.4. Pause Rules

There are no study pause rules. However, if the DSMB requests that the study be paused due to a safety concern, further study vaccination will be suspended, but all other planned procedures relating to safety, reactogenicity, rVE, and immunogenicity assessments will continue as described in the study protocol. The Sponsor will notify the Center for Biologics Evaluation and Research within 48 hours in the event of a study pause.

If a pause is triggered in the study, each participant's study site visit will continue until the EoS. If a pause affects a participant's vaccination visit, the window for that participant's vaccination visit will be suspended until the pause is lifted and vaccination can resume. Once the pause is lifted, vaccination should be reinstated as soon as possible by notifying all investigators.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements.

Any results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1. Demography

Demographic information relating to the participant's sex, age, race, ethnicity, height, weight, and BMI will be recorded at Screening in EDC.

Medical history of each participant will be collected and recorded in EDC. Significant findings that were present prior to the signature of the informed consent will also be included in EDC.

8.2. Efficacy and Immunogenicity Assessments

Immunogenicity assessments are to be performed for Part 1 and Part 2.

Immunogenicity of mRNA-1283.222 vs mRNA-1273.222 will be assessed as a co-primary objective in Part 1 (Table 2). For immunogenicity, blood samples will be collected at timepoints indicated in the SoA (Table 1). Testing will be performed in a laboratory designated by the Sponsor for the following parameters.

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus neutralization assays.
- 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.

Neutralizing antibody responses after vaccination with mRNA-1283.815 and mRNA-1273.815 is an exploratory objective in Part 2.

The rVE of mRNA-1283 vs mRNA-1273 (variant formulations) will be evaluated in a pooled analysis combining data from Part 1 and Part 2 (primary relative vaccine efficacy objective) (Table 3). Active surveillance for COVID-19 and SARS-CoV-2 infection will be performed as outlined in Section 8.3.6.

8.3. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

Part 1: All Participants and Part 2: Adolescents and Previously Unvaccinated Participants

- Solicited local and systemic ARs (Section 10.2.1) that occur during the 7 days following vaccination (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 8.3.5).

Part 1 and Part 2: All Participants

- Unsolicited AEs observed or reported during the 28 days following vaccination. Unsolicited AEs (Section 10.2.1) are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to discontinuation from the study.
- MAAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- AESIs from vaccination on Day 1 through EoS or withdrawal from the study. SAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- Vital sign measurements before and after injection.
- Physical examination findings (if performed).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 8.3.6).
- Details of all pregnancies in female participants will be collected after the start of study vaccine and until the end of their participation in the study. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after the end of the study may not be collected in the clinical database (Section 8.4.5).

The incidence and severity of the above events will be monitored by the blinded study team members.

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.3.1. Physical Examinations

A full physical examination will be performed during the screening period according to standard medical practice, including assessment of vital signs, height, and weight. The information collected will be recorded in the eCRF.

Symptom-directed physical examinations will be performed at all other scheduled timepoints as specified in the SoA (Table 1). Interim physical examinations will be performed at the discretion of the investigator.

On the day of the injection, the arm receiving the study intervention should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as an MAAE.

Treatment of any abnormality observed during physical examination should be performed according to local medical practice outside the study or by referral to an appropriate healthcare provider at the discretion of the investigator.

8.3.2. Vital Signs

Vital sign measurements include the assessment of body temperature, systolic and diastolic blood pressures, heart rate, and respiratory rate. The preferred route of temperature assessment is oral. On study injection day, vital signs will be collected prior to injection and approximately 15 minutes after injection (prior to discharge of the participant from the study site). When applicable, vital sign measurements should be performed before blood collection.

Febrile participants on study injection day (fever is defined as body temperature ≥38.0°C/100.4°F) may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses may be injected at the discretion of the investigator. If fever is clinically concerning, participants should not be dosed.

An abnormal vital sign measurement should be assessed to determine if it meets AE reporting criteria per protocol and reported as an AE in the EDC, if appropriate. The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

Vital signs may be collected at other in-person visits in conjunction with a symptom-directed physical examination. A pulse oximeter measurement may be performed at unscheduled or illness visits, if applicable/available.

8.3.3. Pregnancy Testing

No routine safety laboratory assessments are planned for this study.

A point-of-care urine pregnancy test will be performed at the Screening Visit and before the injection on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's FSH level should be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.

Further details on reporting and follow-up of pregnancy are provided in Section 8.4.5 and Section 10.3.

8.3.4. Safety Phone Calls

A safety phone call is a telephone call made to the participant by trained trial personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls will follow a schedule for each participant, as shown in the SoA (Table 1).

The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to withdrawal from study participation, concomitant medications

associated with those events, and any non-study vaccinations (Section 8.4.2). All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone/remote contact. An unscheduled safety phone call may be triggered if an eDiary record results in identification of a relevant safety event. A safety phone call may trigger an illness or unscheduled visit.

8.3.5. Use of eDiaries

Part 1: All Participants and Part 2: Adolescents and Previously Unvaccinated Participants

At the time of consent, the participants must confirm they will be willing to complete an eDiary (for 7-day reactogenicity). The local and systemic ARs that will be solicited by the eDiary are described in Table 8.

Solicited local and systemic reactogenicity ARs will be collected on the day of each study injection and during the 7 days after study injection (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.4.6.

At the dosing visit, the participant will record data into the eDiary starting approximately 15 minutes after dosing under supervision of the site staff to ensure successful entry of assessments. The 15-minute observation period is an opportunity for site staff to train the participant on eDiary completion requirements. The site staff will perform any retraining as necessary.

At the dosing visit, the participant will be instructed or reminded on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) side as the injection arm(s) during the 7 days after study injection. Daily oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the site staff.

Part 1 and Part 2: All Participants

The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1) for surveillance of COVID-19. Participants will be reminded to call the site immediately if they experience symptoms of COVID-19. If eDiary questions result in identification of relevant safety events according to the study period or symptoms of COVID-19, a follow-up safety call will be triggered. The results of the safety call should be recorded in the appropriate source documentation.

If a participant does not respond to the eDiary questions according to the SoA, site staff will follow-up with the participant.

8.3.6. Assessments for SARS-CoV-2 Infection

Study participants will undergo nasal swab samples routinely, collected for SARS-CoV-2 testing as specified in the SoA (Table 1).

For the duration of the study, if participants experience symptoms of COVID-19 as defined below, then participants will be directed as soon as possible and within 72 hours to obtain a SARS-CoV-2 PCR test at the study site.

Symptoms of COVID-19 include:

- Fever (≥38°C/100.4°F)
- Chills
- Muscle/body aches
- Headache
- Sore throat
- A new, continuous cough
- A loss or change to sense of smell or taste
- Shortness of breath/difficulty breathing
- Fatigue
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

If participants take an approved/authorized SARS-CoV-2 PCR test outside the study site, then participants are required to report the results of the PCR test to the study clinic and to provide a copy of these results.

If participants take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2 (at home or other location) site and the test is positive or equivocal, participants will be required to present to the study site for SARS-CoV-2 PCR testing.

Participants will also be directed to undergo PCR testing if they come into close contact with someone who has known COVID-19 or SARS-CoV-2 infection. Examples include:

- Being within 2 meters (without PPE) for a total of 15 minutes or more
- Providing care at home
- Having direct physical contact
- Sharing eating or drinking utensils
- Being sneezed or coughed upon or getting respiratory droplets on the participant

All PCR-confirmed COVID-19 events (as defined in Table 3) should be captured as MAAEs (unless the definition of an SAE is met) along with relevant concomitant medications, hospitalizations, outpatient medical care, and details about severity, seriousness, and outcome. Clinical information including but not limited to the following should be collected, if applicable: clinical assessment or imaging (including percentage of lung infiltrates), oxygen saturation (SpO_2), respiratory rate, and hospital course including (but not limited to) PaO_2/FiO_2 ratio, respiratory failure, oxygen support, shock, organ dysfunction, and life-sustaining treatment.

Severe COVID-19 (assessed in Part 2) is defined as virologically confirmed SARS-CoV-2 infection with ANY of the following starting 14 days after vaccine injection:

- Clinical signs at rest indicative of severe systemic illness: respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300 mmHg; OR
- Respiratory failure or acute respiratory distress syndrome (requiring high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic BP <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); OR
- Significant acute renal, hepatic, or neurologic dysfunction; OR
- Admission to an intensive care unit or death.

8.4. AEs, SAEs, and Other Safety Reporting

The definitions of unsolicited AEs and solicited ARs can be found in Section 10.2.1. The definitions of SAEs can be found in Section 10.2.2.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following all AEs and SAEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from Screening until EoS at the timepoints specified in the SoA (Table 1).

All unsolicited AEs will be collected from the start of study intervention until Day 29 at the timepoints specified in the SoA (Table 1).

Part 1: All Participants and Part 2: Adolescents or Previously Unvaccinated Participants: All solicited local and systemic ARs will be collected from the start of study intervention through Day 7 as specified in Table 1 and Section 10.2.1.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Part 1: All Participants and Part 2: Adolescents or Previously Unvaccinated Participants.

The eDiaries have specifically been designed for this study. At the time of consent, the participants or participant's parent(s)/legal guardian(s) must confirm they will be willing to complete the eDiary via an application downloaded to their smartphone or via a device that is provided at the time of enrollment. Prior to enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs on Day 1. The eDiaries will include pre-listed AEs (solicited AEs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

Part 1 and Part 2: All Participants

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to the IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE or AESI requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. For example, for reports that are required to be submitted to the European Union, Individual Case Safety Reports will be submitted via the EudraVigilance Clinical Trial Module Gateway.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For expedited reporting purposes, the expectedness of SAEs will be assessed against the investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB for IPs and comparators will be considered unexpected.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

Female participants who have a positive pregnancy test at Screening should not be enrolled. Participants who have a positive pregnancy test at any time during the study should receive no further dosing with IP but should be asked to remain in the study and be followed up for safety. Pregnancy testing is scheduled to occur at Screening and Day 1 (Table 1).

Details of all pregnancies in female participants will be collected after the start of study intervention and until EoS.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (refer to Section 10.2).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 10.2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant-and the neonate, and the information will be forwarded to the Sponsor.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Solicited ARs

Part 1: All Participants and Part 2: Adolescents and Unvaccinated Participants Only

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.3.5). Participants will record such occurrences in the eDiary on the day of each study injection and the 6 subsequent days.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 8, which are modified from the Toxicity Grading Scales 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.

If a participant reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study staff in EDC.

If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event in EDC.

If the participant reported an event that started after the solicited period (ie, beyond 7 days after dosing), it should be recorded as an AE in EDC. Causality for these events will be determined per assessment by the investigator.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff in EDC:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to discontinuation).
- Solicited local or systemic AR lasting beyond 7 days post injection.
- Solicited local or systemic AR that leads to participant discontinuation from study intervention.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

8.4.7. Medically Attended Adverse Events

An MAAE is an AE that leads to a visit to an HCP. This would include visits to a study site for unscheduled/illness assessments (eg, rash assessment, abnormal laboratory follow-up) and visits to HCPs external to the study site (eg, emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured in EDC.

8.4.8. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the Sponsor are required. Such events may require further investigation to characterize and understand them.

AESIs for this protocol are listed in Section 10.4. Additional information for anaphylaxis (Section 8.4.8.1), myocarditis/pericarditis (Section 8.4.8.2), and MIS-C (Section 8.4.8.3) are provided below.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system.

Investigators should report all events that fall into the following categories as an AESI per the reporting processes specified in Section 10.2 (Reporting of SAEs).

8.4.8.1. Anaphylaxis

All suspected cases of anaphylaxis should be recorded as MAAEs and AESIs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. The investigator will report any anaphylaxis event immediately (within 24 hours) and updated case data to the Sponsor within 24 hours of it being available.

For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitive reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:
  - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes
  - **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation
  - **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea
  - **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting

8.4.8.2. Myocarditis and/or Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC Working Case Definitions. The event should also be reported as an SAE if it meets seriousness criteria (Section 10.2.2).

An independent external CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical trials per the CEAC charter, to determine if they meet CDC criteria for “probable” or “confirmed” events (Section 10.1.6.2).

The CDC Working Case Definitions are provided in Section 10.5 as guidance. These definitions are intended to serve as a guide to help reporting of suspected cases of myocarditis, pericarditis, or myopericarditis, but the diagnosis of suspected cases is left to the investigator’s clinical judgment.

8.4.8.3. Multisystem Inflammatory Syndrome in Children

Investigators will also be asked to report, as an AESI, clinical signs/symptoms consistent with the CDC case definition of MIS-C (CDC 2023):

- An individual aged < 21 years presenting with fever (fever ≥38.0°C/≥100.4ºF for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6; elevated neutrophils; reduced lymphocytes; or low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology (non-S protein-based), or antigen test or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Some participants may fulfill full or partial criteria for Kawasaki disease, but it should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Refer to immunogenicity assessments presented in Section 8.2.

8.9. Immunogenicity Assessments

Immunogenicity assessments are presented in Section 8.2.

9. STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analyses and procedures for the study. The details of the statistical analyses will be provided in the SAP. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be identified in the CSR.

9.1. Blinding and Responsibility for Analyses

This study is observer-blind; blinding during the study will be conducted as described in 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 (Section 6.4).

An independent unblinded statistical and programming team who are not involved in study design and conduct will perform the planned interim analyses. A prespecified Sponsor team including biostatistician(s) and statistical programmer(s) will be unblinded to treatment-group level information at the Part 1 (Day 29) interim analysis results. The details regarding roles and corresponding unblinding will be included in the Study Data Blinding Plan.

The Part 1 interim rVE analysis will be reviewed by the DSMB in a closed session and the Sponsor will remain blinded to any interim rVE results. Upon review of interim data, the DSMB will make a recommendation to the Sponsor regarding enrollment based on prespecified rules (Section 9.3). The DSMB otherwise periodically reviews unblinded safety data in closed sessions. Details regarding the DSMB reviews will be provided in the SAP and the DSMB charter.

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

9.2. Statistical Hypotheses

Primary Hypotheses for the 4 co-primary immunogenicity endpoints:

Immunogenicity primary hypotheses testing will be based on the PPIS in Part 1.

1. The null hypothesis H^1_0: Antibody GMT 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 GMR defined as the ratio of GMT of mRNA-1283.222 at Day 29 over the GMT of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).
2. The null hypothesis H^2_0: Antibody 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%.

3. The null hypothesis H^3_0: Antibody GMT 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 GMT of mRNA-1283.222 at Day 29 over the GMT of mRNA-1273.222 at Day 29. The prespecified non-inferiority margin is 1.5 or 0.667 (1/1.5).
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%.

Non-inferiority based on 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% CI of GMR >0.667.

Non-inferiority based on 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 can be used in sensitivity analyses, where baseline refers to pre-booster.

The study is considered to meet the primary immunogenicity objectives if non-inferiority is demonstrated in the 4 co-primary immunogenicity endpoints.

Primary Hypothesis for rVE:

Primary rVE hypothesis testing will be based on the PPSE from Part 1 and Part 2 combined.

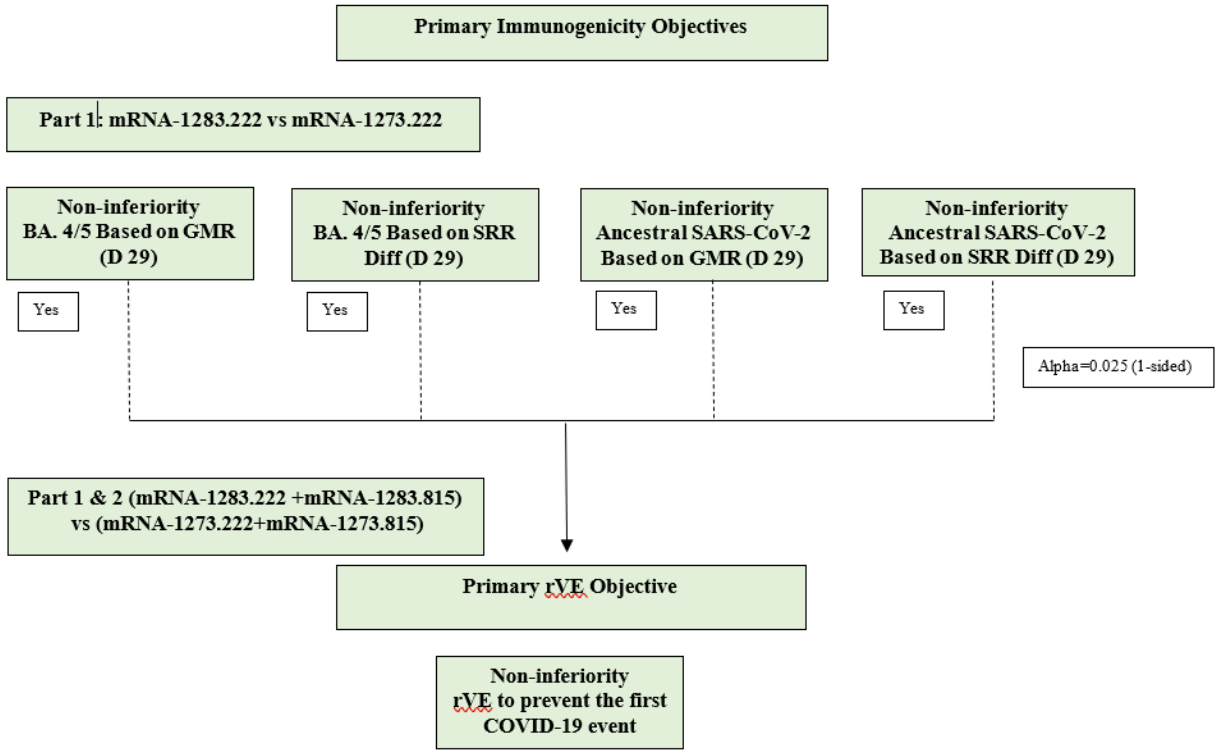
1. The null hypothesis H_0: rVE of mRNA-1283 compared to mRNA-1273 (variant formulation) is inferior to prevent the first occurrence of COVID-19. The prespecified non-inferiority margin is 10%.

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 booster dose, and the null hypothesis is: H_0: rVE ≤-10% (this is equivalent to HR ≥1.1, where rVE = 1-HR).

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, using the PPSE. Section 9.5.2.1 provides details of how to assess non-inferiority under the framework of 2-stage sequential design with sample size re-estimation.

The hypothesis for the rVE endpoint will be tested if all 4 co-primary immunogenicity endpoints are met (Figure 2).

Figure 2: 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.

9.3. Sample Size Determination

The total number of participants to be enrolled is up to approximately 33,574 (Parts 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: 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 (See Sections 9.1 and 10.1.6).

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). The definition of COVID-19 is provided in Table 3. 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.

An interim rVE analysis based on Part 1 COVID-19 event information may be performed when at least 700 COVID-19 events have been confirmed. This analysis will be based on the O'Brien-Fleming boundary methodology for efficacy and futility (O'Brien and Fleming 1979).

The following assumptions support the power calculation:

- Target rVE is 3% (mRNA-1283 over 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 is approximately 10% (including off-study COVID-19 vaccine use which will result to COVID-19 event censoring from the timepoint an off-study COVID-19 vaccine was used).

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 favorable 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).

Sample size of 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 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.

With this sample size, there is at least 90% probability to observe at least one participant reporting an AE if the true rate of AEs is 0.1%, with at least ~10,061 to ~16,787 participants receiving mRNA-1283 variant formulation.

9.4. Analysis Sets

The analysis sets are described in Table 6 for Part 1 and Part 2, as applicable.

Table 6: Analysis Sets

Set	Description
FAS	The FAS consists of all randomized participants who receive the IP. Participants will be analyzed according to their randomized study arm.
PPIS	The PPIS consists of a randomly sampled subset of participants who received the planned dose of study vaccination and have no major protocol deviations that impact key or critical data. Participants will be analyzed according to their randomized study arm. Part 1 PPIS will be the primary analysis set for analyses of immunogenicity unless otherwise specified. A PPIS may be used to support the exploratory immunogenicity endpoint in Part 2.
Solicited Safety Set	The Solicited Safety Set consists of all randomized participants who receive IP and contribute any solicited AR data in Part 1 and adolescents and previously unvaccinated participants in Part 2. 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.
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.

Set	Description
PPSE	The 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.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; PPSE = per protocol set for efficacy; PPIS = per protocol immunogenicity subset.

9.5. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

This section summarizes the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Immunogenicity Analyses

9.5.1.1. Analyses for the Primary Immunogenicity Objectives

The primary immunogenicity objective (prespecified in Part 1 only) is to demonstrate a non-inferior antibody response 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 after the booster injection administered. The primary analysis population for immunogenicity will be the Part 1 PPIS.

The immune response as measured by the serum antibody GMT at Day 29 of mRNA-1283.222 group will be compared to that of mRNA-1273.222 group. An analysis of covariance model will be carried out with the dependent variable of the serum Ab titer at Day 29 and a group variable (mRNA-1283.222 vs mRNA-1273.222) as the fixed variable, adjusted by SARS-CoV-2 status at pre-booster, age group, number of prior boosters, type of primary series and prior booster vaccine if applicable. The GMT will be estimated by the 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 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 each visit will be tabulated.

If a participant receives an off-study COVID-19 vaccine during the study, the participant's immunogenicity data will be censored after the timepoint the participant receives the off-study COVID-19 vaccine.

Success criteria for the hypothesis testing of the serum Ab GMR, ie, non-inferiority criteria, will be implemented. Specifically, if the lower bound of the 95% CI of the GMR is >0.667, non-inferiority of serum antibody GMT of mRNA-1283.222 booster dose compared to mRNA-1273.222 will be demonstrated at one-sided alpha of 0.025.

The non-inferiority of SRR difference of mRNA-1283.222 booster dose compared to mRNA-1273.222 will be demonstrated if the lower bound of the 95% CI of the SRR difference is >-10% with non-inferiority margin of 10% at one-sided alpha of 0.025.

The study would have met the primary immunogenicity objective if non-inferiority is demonstrated based on the 4 co-primary endpoints.

In addition to the primary analysis with PPIS, subgroup analyses will be performed by baseline SARS-CoV-2 infection status, positive and negative.

9.5.1.2. Analyses for the Secondary and Other Immunogenicity Objectives

SARS-CoV-2-specific nAb and bAb are assessed at multiple timepoints in each part of this study. Immunogenicity is a secondary objective in Part 1 and an exploratory objective in Part 2.

For each of the antibodies of interest, eg, levels of SARS-CoV-2-specific nAb and SARS-CoV-2-specific bAb, the GMT or level with corresponding 95% CI at each timepoint, and GMFR of postbaseline/baseline titers or levels with corresponding 95% CI at each postbaseline timepoint will be provided for each arm. The 95% CIs will be calculated based on the t-distribution of the log-transformed values or difference in log-transformed value, and then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each timepoint: number of participants (n), median, minimum, and maximum.

The mixed effect model repeated measure will be used to analyze all post-booster measures for between booster comparison; the model will include treatment group, analysis visit, treatment by visit interaction, adjusted by SARS-CoV-2 status at pre-booster, age group, number of prior boosters, type of primary series and prior booster vaccine if applicable. An unstructured covariance structure will be used to model the within-participant errors. The GMT will be estimated from the model and its corresponding 95% CI will be provided for each group at each post-boost timepoint. The GMR will be estimated from the model and the corresponding 95% CI will be provided at each post-boost timepoint.

9.5.2. Efficacy Analyses

9.5.2.1. Analyses for the Primary rVE Objective

Efficacy analyses will be performed using the FAS and PPSE (Table 6). The primary analysis will be based on the PPSE. Participants will be included in the treatment group to which they were randomized. Efficacy analyses will be based on the Part 1 and Part 2 combined data.

To assess the rVE endpoint as described in Table 3, Cox proportional hazards regression model will be used to estimate HR. The rVE, ie, 1-HR (mRNA-1283 vs mRNA-1273), will be estimated along with the 2-sided 95% CI or alpha-adjusted CI.

The rVE is defined as the percent reduction in the hazard of the first occurrence of COVID-19 starting 14 days after vaccine injection (mRNA-1283 vs mRNA-1273) and will be estimated using 1-HR. 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) based on the PPSE. The stratification factor at randomization, age group (≥12 to <18 years, ≥18 to <65 years or ≥65 years), will be included as the strata variable. SARS-CoV-2 status at pre-injection, number

of prior injections, and type of prior vaccine may be included in the Cox model, if applicable. Efron's method will be used to handle ties.

For the primary rVE endpoint, participants without COVID-19 will be censored at their last assessment date. Potential intercurrent events may include:

- Death unrelated to COVID-19.
- Early COVID-19 up to 14 days after IP administration.
- Off-study COVID-19 vaccine use.

In the estimand of the primary analysis on the rVE endpoint, different strategies will be used for the above three types of intercurrent events based on PPSE. Details can be found in Section 9.6.

For the Part 1 rVE interim analysis, O'Brien-Fleming boundary (O'Brien and Fleming 1979) will be used for efficacy and futility.

If recommended target number of COVID-19 events after the Part 1 rVE interim analysis remains at 2087 events (Section 9.3):

The hypothesis testing H_0: rVE ≤-10% can be evaluated directly using the lower bound of rVE. If the lower bound of the alpha-adjusted CI of rVE >-10% (equivalent to the upper bound of the CI of the HR <1.1). Non-inferiority of preventing the first occurrence of COVID-19 of mRNA-1283.222 injection compared to mRNA-1273.222 will be demonstrated at one-sided alpha of 0.025.

If the DSMB recommendation is to increase from the number of COVID-19 events from 2087 to 3500, the CHW Test (Cui L 1999; Lehmacher 1999) will be used for hypothesis testing at the final 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 first rVE interim analysis, and the sum of n_1, and 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 ≤ conditional power<0.8); $\ddot{n}^*_2$ is the incremental number of events between stage 1 and stage 2; and Z_1 is the test statistics at first rVE interim analysis.

rVE and 95% CI will be provided for the overall rVE estimate.

The CDC COVID-19 definition is the primary definition, and the protocol-defined COVID-19 is the secondary COVID-19 definition (see Table 3 for definitions). The secondary definition will be used in a sensitivity analysis.

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) %

The 95% CI of rVE will be computed using the exact method conditional upon the total number of events adjusted by the total person-time.

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 (years) in each vaccination group.

Person-time is calculated as the total time (years) from randomization to the date of the first occurrence of COVID-19 in participants, and the time from randomization to the date of censoring for participants without event (or who are censored).

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.

9.5.2.2. Analyses for Secondary Objective

The incidence of asymptomatic SARS-CoV-2 infections and the incidence of severe COVID-19 in each vaccine group (starting 14 days after any injection) in Part 1 and Part 2 are secondary endpoints. There is no hypothesis testing for these endpoints. The incidence rates will be provided for each vaccine group, calculated as the number of events divided by the total person-time. Infection incidence rates will also be provided by age groups.

Safety Analyses

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 treatment group (mRNA-1283 and mRNA-1273 [variant formulation]).

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, and physical examination findings.

The number and percentage of participants with any solicited local or systemic AR and any solicited AR during the 7-day follow-up period after study injection by toxicity grade will be assessed. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR. The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by the MedDRA preferred term and system organ class. The number of events of solicited ARs, unsolicited AEs/SAEs, AESIs, and MAAEs will be reported in summary tables accordingly.

Solicited AR events (starting within 7 days after any injection) that are serious or lasting beyond Day 7 after study injection are also reported as unsolicited AEs.

For all other safety parameters, descriptive summary statistics will be provided in the SAP.

9.5.3. Other Exploratory Analyses

Details of exploratory analyses will be described in the SAP before database lock.

9.5.4. Subgroup Analyses

Subgroup analyses will be performed in select subgroups, including but not limited to, the following subgroups:

- Sex
- Age
- Race
- Ethnicity
- SARS-CoV-2 status at Baseline
- Number of prior booster doses
- Geographic region
- Time interval groups (from prior dose to current booster dose)

Details of subgroups analyses will be provided in the SAP.

9.6. Primary Estimands

The estimand for the rVE objective and strategies for handling intercurrent events are summarized in Table 7.

Table 7: 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.
Treatment Condition(s)	Test: mRNA-1283 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 strategy
IcEv2 (early COVID-19)	Hypothetical strategy
IcEv3 (off-study COVID-19 vaccine use)	While on treatment strategy

Objective: To demonstrate the non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulation) to prevent COVID-19	
Rationale for Strategies	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 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.

Abbreviations: COVID-19 = coronavirus disease 2019; HR = hazard ratio; IcEv = intercurrent event; mRNA = messenger ribonucleic acid; PCR = polymerase chain reaction; PPSE = per protocol set for efficacy; rVE = relative vaccine efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

9.7. Secondary Estimands

Secondary estimands are not evaluated in this study.

9.8. Planned Analyses

9.8.1. Interim Analyses

For Part 1, an interim analysis of safety and immunogenicity will be performed after all participants, or a subset of participants, have been followed up for at least 29 days after the injection. An interim rVE analysis will also be performed.

For Part 1 and Part 2 combined, an interim rVE analysis will be performed when COVID-19 events reach their target according to the decision rules of Section 9.3.

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

9.8.2. 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 final CSR, including individual listings.

Additional information about all study analyses may be provided in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their LAR and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They or their LARs will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or their LAR.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.1.4. Recruitment Strategy

Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate.

Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site. Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB/IEC.

10.1.5. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

10.1.6.1. Data Safety Monitoring Board

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

After each data review meeting, 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 (Sections 9.3 and 9.8.1).

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 and analysis plan.

10.1.6.2. Cardiac Event Adjudication Committee

An independent CEAC consisting of cardiologists will review suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they meet CDC criteria of “probable” or “confirmed” event, and to assess severity. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

10.1.7. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), etc., as well as some national registries.

In addition, results from clinical trials are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For

those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in clinical studies sponsored by the Sponsor is ensured. Details on data sharing criteria and the process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent/assent forms, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the

safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. APPENDIX 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- 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: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

- Solicited ARs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.
- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
  - Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
  - Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participant/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the required form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 10.2.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. The intensity grading scale used in this trial is presented in Table 8.

Table 8: Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

Abbreviations: EDC = electronic data capture.
Note: Events listed above but starting >7 days post study injection will be recorded in EDC. Causality for each event will be determined per assessment by the investigator.
Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship using the following classification:

- **Not related:** There is not a reasonable possibility of a relationship to the study intervention. Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention.
- **Related:** There is a reasonable possibility of a relationship to the study intervention. There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to the Sponsor or designee via an EDC Tool

The primary mechanism for reporting an SAE to the Sponsor or designee will be the EDC.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC has been taken offline, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor or designee via Paper Data Collection Tool

If the EDC is unavailable at the time of reporting an SAE, the paper data collection tool method should be used to report the SAE within 24 hours.

Initial notification via email does not replace the need for the investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.

SAE reports should be emailed to drugsafety@modernatx.com.

10.3. APPENDIX 3: Contraceptive and Barrier Guidance

10.3.1. Definitions

Women in the following categories are considered women of childbearing potential (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

          Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
    - If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.3.2. Contraception Guidance

Adequate female contraception is defined as consistent and correct use of a regulatory agency-approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide.
- Intrauterine device.
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route.

- Sterilization of a female participant's monogamous male partner prior to entry into the study.

Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

10.4. APPENDIX 4: Adverse Events of Special Interest

The investigator's medical judgment must be applied to assess an event as an AESI, as most AESIs are based on medical concepts.

Table 9 describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance during Part 1. Table 10 describes the events/medical concepts that are of interest in COVID-19 during Part 2. These tables do not provide a comprehensive list of terms. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per protocol, even when they occur during/following COVID infection.

Please note: COVID-19 itself is not an AESI.

Table 9: Adverse Events of Special Interest– Part 1

Medical Concept	Additional Notes
Anosmia, Ageusia	New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute Thyroiditis	Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) DOES NOT INCLUDE new onset of chronic thyroiditis
Acute Pancreatitis	New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	Any event of appendicitis
Rhabdomyolysis	New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
ARDS	New onset of ARDS/respiratory failure due to acute inflammatory lung injury DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation Disorders	New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (eg, stroke, DVT, pulmonary embolism, disseminated intravascular coagulation, etc.)

Medical Concept	Additional Notes
Acute Cardiovascular Injury	New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by ECG (eg, atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute Kidney Injury	New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc; Increase in serum creatinine by ≥0.3 mg/dl (or ≥26.5 μmol/L) within 48 hours; **OR** Increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred within prior 7 days
Acute Liver Injury	New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc; >3-fold elevation above the upper normal limit for alanine aminotransferase or aspartate aminotransferase; OR >2-fold elevation above the upper normal limit for total serum bilirubin or gamma glutamyl transferase or alkaline phosphatase
Dermatologic Findings	Chilblain-like lesions Single organ cutaneous vasculitis Erythema multiforme Bullous rashes Severe cutaneous ARs, such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, fixed drug eruptions, and necrotic or exfoliative reactions
Systemic Inflammatory Syndromes	MIS-A or MIS-C Kawasaki's disease Hemophagocytic lymphohistiocytosis
Thrombocytopenia	Platelet count < 150×10^9/L (thrombocytopenia) New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome

Medical Concept	Additional Notes
Acute Aseptic Arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR DOES NOT INCLUDE new onset of chronic arthritic conditions
New Onset of or Worsening of Neurologic Disease	Immune-mediated neurological disorders Guillain-Barre Syndrome Acute disseminated encephalomyelitis Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/encephalomyelitis Aseptic meningitis Seizures/convulsions/epilepsy Narcolepsy/hypersomnia
Anaphylaxis	Anaphylaxis associated with study intervention administration
Other Syndromes	Fibromyalgia Postural orthostatic tachycardia syndrome Chronic fatigue syndrome Myalgic encephalomyelitis Post viral fatigue syndrome Myasthenia gravis

Abbreviations: AR = adverse reaction; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; ECG = electrocardiogram; HELLP = hemolysis, elevated liver enzymes, and low platelet count; MIS-A = multisystem inflammatory syndrome in adults; MIS-C = multisystem inflammatory syndrome in children; PCR = polymerase chain reaction.

Table 10: Adverse Events of Special Interest– Part 2

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset of anosmia or ageusia idiopathic etiology. • DOES NOT INCLUDE anosmia or ageusia associated with COVID-19, sinus/nasal congestion, congenital, or traumatic etiologies.
Subacute Thyroiditis	• Acute inflammatory disease of the thyroid (immune-mediated or idiopathic). • DOES NOT INCLUDE new onset of chronic thyroiditis.
Acute Pancreatitis	• New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	• Any event of appendicitis.
Rhabdomyolysis	• New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute Respiratory Distress Syndrome (ARDS)	• New onset of ARDS/respiratory failure due to acute inflammatory lung injury. • DOES NOT INCLUDE nonspecific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload.
Coagulation Disorders	• New onset of thrombosis, thromboembolic event, or nontraumatic hemorrhage/bleeding disorder (eg, stroke, DVT, pulmonary embolism, disseminated intravascular coagulation [DIC], etc.).
Acute Cardiovascular Injury	• New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by ECG (eg, atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. • DOES NOT INCLUDE transient sinus tachycardia/bradycardia, nonspecific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute Kidney Injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc.;

Medical Concept	Additional Notes
	• Increase in serum creatinine by ≥0.3 mg/dl (or ≥26.5 µmol/L) within 48 hours; OR – Increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred within prior 7 days.
Acute Liver Injury	• New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc; • >3-fold elevation above the upper normal limit for ALT or AST; OR • >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP.
Dermatologic Findings	• Chilblain-like lesions. • Single organ cutaneous vasculitis. • Erythema multiforme. • Bullous rashes. • Severe cutaneous adverse reactions, such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions.
Systemic Inflammatory Syndromes	• Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C). • Kawasaki's disease. • Hemophagocytic lymphohistiocytosis (HLH).
Thrombocytopenia	• Platelet count $<150 \times 10^9$/L (thrombocytopenia). • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome.
Acute Aseptic Arthritis	• Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. • DOES NOT INCLUDE new onset of chronic arthritic conditions.
New Onset of or Worsening of Neurologic Disease	• Immune-mediated neurological disorders. • Guillain-Barre Syndrome. • Acute disseminated encephalomyelitis (ADEM). • Peripheral facial nerve palsy (Bell's palsy).

Medical Concept	Additional Notes
	• Transverse myelitis. • Encephalitis/encephalomyelitis. • Aseptic meningitis. • Seizures/convulsions/epilepsy. • Narcolepsy/hypersomnia.
Anaphylaxis	• Anaphylaxis associated with study drug administration.
Other Syndromes	• Fibromyalgia. • Postural orthostatic tachycardia syndrome. • Chronic fatigue syndrome. • Myalgic encephalomyelitis. • Post viral fatigue syndrome. • Myasthenia gravis. • Capillary leak syndrome (new diagnosis or flare up in participants with prior history of capillary leak syndrome).

Abbreviations: AR = adverse reaction; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; ECG = electrocardiogram; HELLP = hemolysis, elevated liver enzymes, and low platelet count; MIS-A = multisystem inflammatory syndrome in adults; MIS-C = multisystem inflammatory syndrome in children; PCR = polymerase chain reaction.

10.5. APPENDIX 5: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 11 as guidance.

Table 11: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
	Probable Case	**Confirmed Case**
Acute myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms:* Chest pain, pressure, or discomfort Dyspnea, shortness of breath, or pain with breathing Palpitations Syncope	Presence of ≥1 new or worsening of the following clinical symptoms:* Chest pain, pressure, or discomfort Dyspnea, shortness of breath, or pain with breathing Palpitations Syncope
	OR infants and children aged <12 years might instead have ≥2 of the following symptoms: Irritability Vomiting Poor feeding Tachycardia Lethargy	**OR** infants and children aged <12 years might instead have ≥2 of the following symptoms: Irritability Vomiting Poor feeding Tachycardia Lethargy
	AND ≥1 new finding of: Troponin level above upper limit of normal (any type of troponin). Abnormal ECG or EKG or rhythm monitoring findings consistent with myocarditis§. Abnormal cardiac function or wall motion abnormalities on echocardiogram. cMRI findings consistent with myocarditis.	**AND** ≥1 new finding of: Histopathologic confirmation of myocarditis†. cMRI findings consistent with myocarditis¶ in the presence of troponin level above upper limit of normal (any type of troponin).
	AND	**AND**
	No other identifiable cause of the symptoms and findings.	No other identifiable cause of the symptoms and findings.

Condition	Definition	
	Probable Case	**Confirmed Case**
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: Acute chest pain†† Pericardial rub on examination New ST-elevation or PR-depression on EKG New or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for participants who meet criteria for both myocarditis and pericarditis.	

Abbreviations: CDC = Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

Note: An independent CEAC (see Section 10.1.6.2) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study vaccine assignment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† Using the Dallas criteria (Aretz et al 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of: 1) ST-segment or T-wave abnormalities; 2) paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) atrioventricular nodal conduction delays or intraventricular conduction defects.

¶ Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Reference: Gargano et al 2021.

10.6. APPENDIX 6: Protocol Amendment History

The Protocol Amendment Summary of Change Table for the current amendment is located directly before the table of contents.

Amendment 2: 08 Aug 2023

This amendment is considered to be nonsubstantial because it impacts neither the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the change is to increase the sample size to allow enrollment of approximately 1000 adolescents. The amendment also incorporates 2 Administrative Change Letters and other clarifications.

Section # and Name	Description of Change	Brief Rationale
1.1 Protocol Synopsis	Incorporates the amendment changes from the body text.	Consistency in the document.
1.3 Schedule of Assessments	Clarified Footnote b and g to ensure a nasal swab is collected on routine visits and when there is an illness.	Ensure primary endpoint (rVE) of COVID-19 is captured (Administrative Change 1)
4.1 Overall Design; 5.0 Study Population; 9.3 Sample Size Determination	Changed from up to 10,748 to approximately 11,500 participants to be enrolled.	Not to limit enrollment up to 10,748 but to enroll approximately 11,500 participants (Administrative Change 2) and achieve a sample size of approximately 1000 adolescents.
4.2 Scientific Rationale for Study Design	Clarified that a nasal swab for PCR SARS-CoV-2 testing is to be obtained for routine visits as well as an illness visit.	SARS-CoV-2 testing supports the relative vaccine efficacy objective.
9.3 Sample Size Determination	Increased the dropout rate assumption from 10% to 15%.	To account for the potential COVID-19 vaccination outside of the study.
9.4 Analysis Sets	The PPSI (per protocol set for immunogenicity) analysis set was changed to PPIS and consists of a randomly sampled subset of trial participants. The PPSI Neg subset was removed.	To more closely align with the sample size justification in Section 9.3.
9.5.1.1 Analyses for the Primary Immunogenicity Objective	Describe subgroup analysis by baseline SARS-CoV-2 infection status.	To evaluate antibody response in participant subgroups of (with and without prior SARS-CoV-2 infection).

Section # and Name	Description of Change	Brief Rationale
10.1.1 Regulatory and Ethical Considerations	Changed ICG to ICH	Corrected a typographical error

Amendment 1: 02 May 2023

Overall Rationale for the Amendment

This amendment was considered to be substantial as it revised the relative vaccine efficacy (rVE) objective to a primary study objective with an rVE non-inferiority margin (mRNA-1283.222 vs. mRNA-1273.222) of 15%. The change includes a target sample size increase of up to 10,748 participants. It also contained administrative changes and clarifications.

Section # and Name	Description of Change	Brief Rationale
1.1 Protocol Synopsis	Incorporates the amendment changes from the body text.	Consistency in the document.
1.2 Study Schema	The study population was updated to match the inclusion criteria.	As per Administrative Change Letter 1.
1.3 Schedule of Assessments	Headers added for the visit number, month, and type (clinic or safety [telephone] call).	To be consistent with other Schedule of Assessments from the Sponsor.
	Changed the requirement for PCR testing to occur within 24 hours to 72 hours. Allow Baseline (Day 1) testing to occur up to 3 days prior to Day 1.	Provides flexibility for the participants without affecting the integrity of the study.
3 Objectives and Endpoints 9.5.2.1 Analysis for the Primary rVE Objective	Changed the non-inferior rVE from a key secondary endpoint to a primary endpoint.	To demonstrate non-inferiority in rVE (mRNA-1283 vs mRNA-1273) with a more stringent margin.
	Clarified that the CDC definition for COVID-19 will be used as the primary definition. The secondary definition of the protocol-defined COVID-19 definition.	The CDC definition is an updated definition for COVID-19 that requires virologic confirmation and the presence of at least one clinical symptom.
4.1 Overall Design 5 Study Population	The number of participants was increased to at least 6000 and up to 10,748. Each treatment group would enroll up to 5374 participants.	To demonstrate non-inferiority in rVE (mRNA-1283 vs mRNA-1273) with a more stringent margin.
5.1 Inclusion Criteria No. 6	Clarified that documentation of prior COVID-19 vaccine is required.	Good Clinical Practice Documentation. As per Administrative Change Letter 2.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria No. 17	Decreasing the time period for a diagnosis of malignancy from 10 years to 5 years.	Provide more flexibility for the participant without affecting participant safety or the integrity of the study.
6.1 Study Interventions Administered 6.2.2 Clinical Study Material Administered	Allows for a thigh injection.	Provide more flexibility for the participant without affecting participant safety or the integrity of the study.
8.2 Efficacy and Immunogenicity Assessments, 9.5.2 Efficacy Analysis and 9.6 Primary Estimands	rVE will be assessed as the primary endpoint instead of key secondary endpoint.	To demonstrate non-inferiority in rVE (mRNA-1283 vs mRNA-1273) with a more stringent margin.
8.3.6 Assessments for SARS-CoV-2 Infection	Updated the requirement for participants to obtain PCR testing to 72 hours if symptomatic.	Provides flexibility for the participants without affecting the integrity of the study.
9.2 Statistical Hypotheses	The primary hypothesis for the rVE was changed to primary endpoint from key secondary endpoint and the non-inferiority margin changed from 20% to 15 %. The testing strategy was updated.	To demonstrate non-inferiority in rVE (mRNA-1283 vs mRNA-1273) with a more stringent margin.
9.3 Sample Size Determination	The number of participants was increased to at least 6000 and up to 10,748. Each treatment group would enroll up to 5374 participants. The non-inferiority margin was changed to achieve 80% power.	To demonstrate non-inferiority in rVE (mRNA-1283 vs mRNA-1273) with a more stringent margin.
10.2.4 Reporting of SAEs	If EDC is unavailable, then paper data collection should be used to report an SAE within 24 hours.	To ensure SAE reporting within 24 hours.

11. REFERENCES

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr., et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3-14.

Brouwer PJM, Caniels TG, van der Straten K, Snitselaar JL, Aldon Y, Bangaru S, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. Science. 2020 Aug 7;369(6504):643-50.

Centers for Disease Control and Prevention (CDC). Multisystem inflammatory syndrome: Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C) [Internet]. 2023 [updated 2023 Jan 03; cited 2023 Dec 19]. Available from: https://www.cdc.gov/mis/mis-c.html

Chen WH, Tao X, Agrawal AS, Algaissi A, Peng B-H, Pollet J, et al. Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with aluminum hydroxide induces protective immunity and reduces immune enhancement. Vaccine. 2020 Nov 3;38(47):7533-41.

Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999 Sep;55(3):853-7.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 2022 Oct 26] [10 screens]. Available from: https://www.fda.gov/media/73679/download.

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021 Jul 9;70(27):977-82.

Greaney AJ, Loes AN, Crawford KHD, Starr TN, Malone KD, Chu HY, et al. Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe. 2021 Mar 10;29(3):463-76.e6.

Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999. Dec;55(4):1286-90.

Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV 2-spike. Nature. 2020 Aug;584(7821):450-6.

Lv Z, Deng Y-Q, Ye Q, Cao L, Sun C-Y, Fan C, et al. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Science. 2020 Sep 18;369(6510):1505-9.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statist. Med. Dec 2011; 30 (28); 3267 -84.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-56. doi:10.2307/2530245

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84.

World Health Organization (WHO). Weekly epidemiological update on COVID-19 [Internet]. Geneva, Switzerland: WHO; 2021 Aug 10 [cited 2021 Aug 20]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---10-august-2021\

Yang J, Wang W, Chen Z, Lu S, Yang F, Bi Z, et al. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. Nature. 2020 Oct;586(7830):572-7.

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations – a postmarketing surveillance review. Eur J Pediatr. 2002 Jan;161(1):21-5.

Signature Page for VV-CLIN-008478 v5.0

2nd Approval	PPD 21-Dec-2023 20:31:00 GMT+0000

Signature Page for VV-CLIN-008478 v5.0