CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine
Protocol Number:	mRNA-1273-P305 Amendment 2
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number:	EudraCT: 2022-000063-51
Date of Protocol Amendment 2:	26 Aug 2022
Date of Protocol Amendment 1:	03 Mar 2022
Date of Original Protocol:	26 Jan 2022

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine
Protocol Number:	mRNA-1273-P305 Amendment 2
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Protocol accepted and approved by:

See eSignature and date signed on the last page of this document.

PPD

Date

ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine" and the most recent version of the 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 government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without independent ethics committee (IEC) approval except to eliminate an immediate risk to participants.

I agree to administer study vaccine only to participants under my personal supervision or the supervision of a subinvestigator. I will not supply study vaccine 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 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 and ICH E6(R2) GCP guidelines.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	26 Aug 2022
Amendment 1	03 Mar 2022
Original Protocol	26 Jan 2022

Amendment 2, 26 Aug 2022: Current Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment:

Following authorization of the messenger ribonucleic acid (mRNA)-1273.214 booster in the United Kingdom, this amendment will incorporate an optional unblinding for participants who report eligibility to receive an additional coronavirus disease 2019 (COVID-19) booster outside of the study.

The summary of changes table provided below describes the major changes made to Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. The synopsis of the protocol has been modified to correspond to changes in the body of the protocol. Minor copy edits and administrative updates were made throughout the protocol to align with new content as well as for clarity, readability, consistency, and/or accuracy.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
3 (Objectives and Endpoints)	Deleted secondary objective in Table 3 and Table 4 for evaluating immunogenicity of messenger ribonucleic acid (mRNA)-1273.529 or mRNA-1273.214 booster administered in Part 1 or Part 2 of the study as a 3rd or 4th dose	Removed objective since only a few participants were randomized in either part to receive a booster as the 3rd dose
	Modified Table 4 to remove the Month 6 timepoint from all primary	Optional unblinding to occur after Month 3 visit resulting in Month 6 and

Section # and Name	Description of Change	Brief Rationale
	and secondary objectives and endpoints in Part 2	subsequent visits to fall under open-label, observational study Phase B for unblinded participants
	Added exploratory objective to Table 4 to evaluate immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a 4th dose study vaccine in participants at Month 6	To account for assessing immunogenicity in the Part 2 participants who are unblinded or remain blinded
4 (Study Design)	Modified the study design to include 2 Phases for each part: the randomized, blinded phase (Phase A) and the open-label, observational phase (Phase B)	Two phases were included for each part to differentiate between the original, observer-blind phase of the study (Phase A) and the open-label, observational Phase B for eligible unblinded participants to obtain an additional booster outside of the study
6.2 (Randomization and Blinding), 8.5 (Randomization)	Updated text to reflect that randomization occurred during the original, observer-blinded Phase A	Added to clarify that Phase A was the phase during which randomization occurred
6.2 (Randomization and Blinding), Section 9.1 (Blinding and Responsibility for Analyses)	Updated text in accordance with Section 6.3.7	For alignment
6.3.7 (Unblinding)	Updated section to describe optional unblinding for participants who report eligibility for an additional booster outside of the study	Provided clarification of optional unblinding plan

Section # and Name	Description of Change	Brief Rationale
6.5.3 (Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant from Per-protocol Analyses)	Added text, "Any COVID-19 vaccine received outside of the study after the study vaccination"	For clarification
8.9.2 (Assessments for SARS-CoV-2 Infection)	Updated text describing assessments for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection	For clarification
9 (Statistical Analysis Plan)	Updated text in relevant sections and Table 10 in accordance with Section 3, Section 4 and Section 6.3.7	For alignment

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Products: mRNA-1273.529, mRNA-1273.214

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

Protocol Number: mRNA-1273-P305, Amendment 2

Study Duration: Approximately 13 months

Phase of Development: Phase 2/3

Estimated Date First Participant Enrolled: 07 Feb 2022

Estimated Date Last Participant Completed: 07 Apr 2023

Site Locations: Multicenter study in the UK

Objectives and Endpoints

Part 1: mRNA-1273.529 and mRNA-1273

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• Geometric mean titer (GMT) of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration
To evaluate the safety and reactogenicity of mRNA-1273.529 and	• Solicited local and systemic reactogenicity ARs during a 7-day follow up period after vaccination

mRNA-1273 administered as a booster dose	• Unsolicited AEs during the 28-day follow-up period after vaccination • SAEs, medically attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (AESIs) from Day 1 to end of study
Secondary	
Key Secondary	
To demonstrate superiority of the immune response of mRNA-1273.529 compared to mRNA-1273 administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• GMT of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration
Other Secondary	
To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against both the B.1.1.529 and the prototype strain at all evaluable time points	• GMT of mRNA-1273.529 and mRNA-1273 against both the B.1.1.529 and the prototype strain at all evaluable time points after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against both the B.1.1.529 and the prototype strain at all evaluable time points after study vaccine administration
To evaluate the seroresponse rate (SRR) of mRNA-1273.529 and mRNA-1273 boosters administered as a 4th dose	• SRR against the B.1.1.529 strain • SRR against the prototype strain
Exploratory Objectives	
To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.529 booster or mRNA-1273 booster	Reverse transcriptase polymerase-chain reaction (RT-PCR)-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants based on the following criteria: • Protocol-defined COVID-19 case definition o The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough,

	shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND o The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR • Center for Disease Control (CDC) defined COVID-19 definition based on the CDC criteria: the presence of one of the CDC listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample • Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment
To evaluate the immunogenicity of mRNA-1273.529 booster against other variant strains	• GMT of mRNA-1273.529 against other variant strains (eg, Alpha, Beta, Delta) after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against other variant strains after study vaccine administration • GMFR of mRNA-1273.529 against other variant strains after study vaccine administration • SRR against other variant strains
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; GMFR = geometric mean fold rise; GMR = geometric mean titer ratio; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

Part 2: mRNA-1273.214 and mRNA-1273

Objectives	Endpoints
Primary	

To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• Geometric mean titer (GMT) of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration
To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the prototype strain at Day 29 or Month 3	• GMT of mRNA-1273.214 and mRNA-1273 against the prototype strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Day 29 or Month 3 after study vaccine administration
To demonstrate superiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• GMT of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration
To evaluate the safety and reactogenicity of mRNA-1273.214 and mRNA-1273 administered as a booster dose	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination • Unsolicited AEs during the 28-day follow-up period after vaccination • SAEs, medically attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (AESIs) from Day 1 to end of study
Secondary	
To evaluate the seroresponse rate (SRR) of mRNA-1273.214 and mRNA-1273 boosters administered as a 4th dose	• SRR against the B.1.1.529 strain • SRR against the prototype strain

To evaluate the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against other variant strains at Day 29 or Month 3	• GMT of mRNA-1273.214 and mRNA-1273 against other variant strains at Day 29 or Month 3 • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against other variant strains at Day 29 or Month 3 • SRR against other variant strains
To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.214 booster or mRNA-1273 booster	Reverse transcriptase polymerase-chain reaction (RT-PCR)-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants based on the following criteria: • Protocol-defined COVID-19 case definition o The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND o The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. • Center for Disease Control (CDC) defined COVID-19 definition based on the CDC criteria: the presence of one of the CDC listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample • Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment
Exploratory Objectives	
To evaluate cellular immunogenicity in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of T-cells and B-cells after vaccination
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates

To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a 4th dose study vaccine in participants at Month 6	• GMT of mRNA-1273.214 against both the B.1.1.529 and the prototype strain at Month 6 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Month 6 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Month 6 after study vaccine administration • GMFR of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 and prototype strain at all evaluabletimepoints after study vaccine administration • SRR against both the B.1.1.529 and prototype strain at Month 6

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; GMFR = geometric mean fold rise; GMR = geometric mean titer ratio; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

Overall Study Design

The study is a Phase 2/3, 2-part, randomized, observer-blind, active-controlled, multicenter study to evaluate the immunogenicity and safety of mRNA-1273.529 and mRNA-1273.214 booster vaccine in medically stable individuals 16 years and older. The mRNA-1273.529 vaccine contains mRNAs encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). The mRNA-1273.214 vaccine contains mRNAs encoding for both the S-2P of the SARS-CoV-2 Wuhan Hu-1 strain and the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529), formulated in the same LNP.

The study consists of 2 parts with 2 phases each:

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

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

vaccine as the 4th dose. The potential number of participants in each arm and the randomization ratio can be found in the table below.

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

Part 1: Study Arm and Dose Levels

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

Abbreviations: mRNA = messenger ribonucleic acid; N = number.
[a] Part 1 will end enrollment when Part 2 starts enrollment. The number of participants in Part 1 will be determined by the start date of Part 2.

Part 2: Study Arm and Dose Levels

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

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

All participants will have previously received 2 or 3 doses of an authorized/approved COVID-19 vaccine. Participants who previously received 2 doses of a COVID-19 vaccine as a primary series will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the third dose, and participants who have previously received a primary series and 1 booster dose will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the 4th dose. Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine as the 3rd dose of a COVID-19 vaccine. Participants who will receive the 3rd dose as part of the study may have previously received 2 doses of a mRNA or a non-mRNA COVID-19 vaccine (a mixed approach is acceptable).

Medically stable individuals, ages 16 and above (to include 2 age groups: 16 to < 65 and ≥ 65 years) 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 10 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 polymerase chain reaction (PCR) within 90 days prior to enrollment will be 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 (up to 28 days before the Day 1 visit), Vaccination Visit at Day 1 and subsequent study visits on Day 8 (for a subset of participants in Part 2 of the study), Day 29 (Month 1), Day 85 (Month 3), Day 179 (Month 6), and Day 359 (Month 12), with up to 13 months of study participation in each part of the study. Unscheduled visits for potential symptoms of COVID-19 will include PCR testing.

Safety Oversight:

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and CRO medical monitor, as well as safety reviews by an unblinded Data and Safety Monitoring Board (DSMB). The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB, composed of external, independent subject matter experts, including an unblinded statistician, will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

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

Number of Participants:

Part 1: Approximately 600-1000 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 μg of mRNA-1273.529 or 50 μg of mRNA-1273 (active control).

Part 2: Approximately 2,924 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.214 or 50 µg of mRNA-1273 (active control).

Study Eligibility Criteria:

Inclusion Criteria:

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, at least 16 years of age at the time of consent (Screening Visit).
2. Investigator's assessment that the participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized (Section 11.2). A follicle stimulating hormone (FSH) level should be measured at the discretion of the investigator to confirm postmenopausal status, if necessary.
5. 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.
6. Has received 2 prior doses of one of the following approved/authorized COVID-19 vaccines: Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, Janssen. A heterologous vaccine regimen is acceptable.
7. Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine (Moderna or Pfizer/BioNTech) as the 3rd dose of a

COVID-19 vaccine. Participants who will receive the 3rd dose as part of the study may have previously received 2 doses of an approved/authorized mRNA or a non-mRNA COVID-19 vaccine (a heterologous vaccine regimen is acceptable).

Exclusion Criteria:

Participants meeting any of the following criteria, unless noted otherwise, will be excluded from the study:

1. Had close contact (without personal protective equipment [PPE]) as defined by the CDC in the past 14 days to someone diagnosed with SARS-CoV-2 infection or COVID-19 within 10 days of the close contact. 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 by an authorized/approved lateral flow/rapid antigen or PCR test within 90 days of Screening or later.
4. Has received a COVID-19 vaccine within 90 days of the Screening Visit.
5. Has received a total of 4 doses or more of COVID-19 vaccine.
6. Has received a COVID-19 vaccine at a dose different from the authorized/approved dose.
7. 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.
8. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease requiring immunosuppressive treatment or other immunosuppressive condition.
9. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
10. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any components of mRNA vaccine.

11. Reported history of bleeding disorder that is considered a contraindication to intramuscular (IM) injection or phlebotomy.
12. 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.
13. 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.
14. Has received or plans to receive any licensed vaccine ≤ 28 days prior to the study injection (Day 1) or plans to receive a licensed vaccine within 28 days after the study injection (with the exception that approved seasonal influenza vaccine may be received by at least 7 days and preferably 14 days apart from the study injection).
15. Has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive during the study.
16. Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer).
17. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
18. 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.
19. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

Study Treatments:

The vaccines to be administered in this study are described in the table below.

Investigational Product and Active Comparator Administered

Study Arm:	mRNA-1273	mRNA-1273.529	mRNA-1273.214
Intervention Name:	mRNA-1273 (aka, Moderna COVID-19 vaccine)	mRNA-1273.529	mRNA-1273.214

Type:	Vaccine	Vaccine	Vaccine
Dosage Level(s):	50 µg (mRNA)	50 µg (mRNA)	50 µg (mRNA)
Route of Administration:	IM injection	IM injection	IM injection
Physical Description:	Sterile liquid for injection, white-to-off-white dispersion	Sterile liquid for injection, white-to-off-white dispersion	Sterile liquid for injection, white-to-off-white dispersion
Source:	Sourced locally by the sites	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	mRNA-1273 will be provided in its commercial presentation	mRNA-1273.529 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.	mRNA-1273.214 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid.

mRNA-1273 is a LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2.

mRNA-1273.529 contains mRNA CX-031302 encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). mRNA-1273 contains mRNA CX-024414 encoding for the S-2P of Wuhan-Hu-1. mRNA-1273.529 and mRNA-1273 each consists of mRNAs formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG 2000-DMG.

mRNA-1273.214 contains CX-024414, the mRNA that encodes for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2, and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant. The formulated mRNAs are mixed in a 1:1 ratio. mRNA-1273.214 consists of each mRNA formulated in a mixture of four lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG 2000-DMG.

mRNA-1273.529, mRNA-1273.214, and mRNA-1273 will be administered at a 50 µg dose level as an IM injection into the deltoid muscle on Day 1.

Procedures and Assessments:

Immunogenicity Assessments:

Blood samples will be collected for the following parameters:

- Serum binding antibody (bAb) level against SARS-CoV-2 as measured by ligand binding assay specific to the SARS-CoV-2 S protein and the S protein receptor-binding domain (RBD).
- Serum neutralizing antibody (nAb) level against SARS-CoV-2 as measured by pseudovirus neutralization assays.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

Safety Assessments:

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

- Solicited local and systemic adverse reactions (ARs) 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.
- Unsolicited adverse events (AEs) observed or reported during the 28 days following vaccination. Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to withdrawal from the study.
- Medically attended AEs (MAAEs) from vaccination on Day 1 through end of study (EoS) or withdrawal from the study.
- AEs of special interest (AESIs) from vaccination on Day 1 through EoS or withdrawal from the study.
- Serious AEs (SAEs) from vaccination on Day 1 through EoS or withdrawal from the study.
- Vital sign measurements before and after vaccination.
- Physical examination findings (if performed).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.
- 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.

Efficacy Assessments:

Vaccine efficacy will be assessed as an exploratory endpoint in Part 1 and as a secondary endpoint in Part 2 of this study. Active surveillance for COVID-19 and SARS-CoV-2 infection will be performed in both parts of the study.

Statistical Methods:

Statistical Hypotheses:

Part 1:

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

Primary Hypotheses:

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

Key Secondary Hypothesis:

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

For the primary objective of immune response, hypotheses testing based on participants receiving the 4th dose, alpha of 0.05 (2-sided) will be allocated to the 2 time points: alpha of 0.01 (2-sided) will be allocated to Day 29, alpha of 0.04 (2-sided) will be allocated to Month 3.

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Day 29 will be assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.01. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain is demonstrated, ie, the lower bound of the 99% confidence interval (CI) of the GMT ratio of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5).

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Month 3 will be assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.04. The primary immunogenicity objective is considered met if non-inferiority against the

B.1.1.529 strain is demonstrated, ie, the lower bound of the 96% confidence interval (CI) of the GMT ratio of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5).

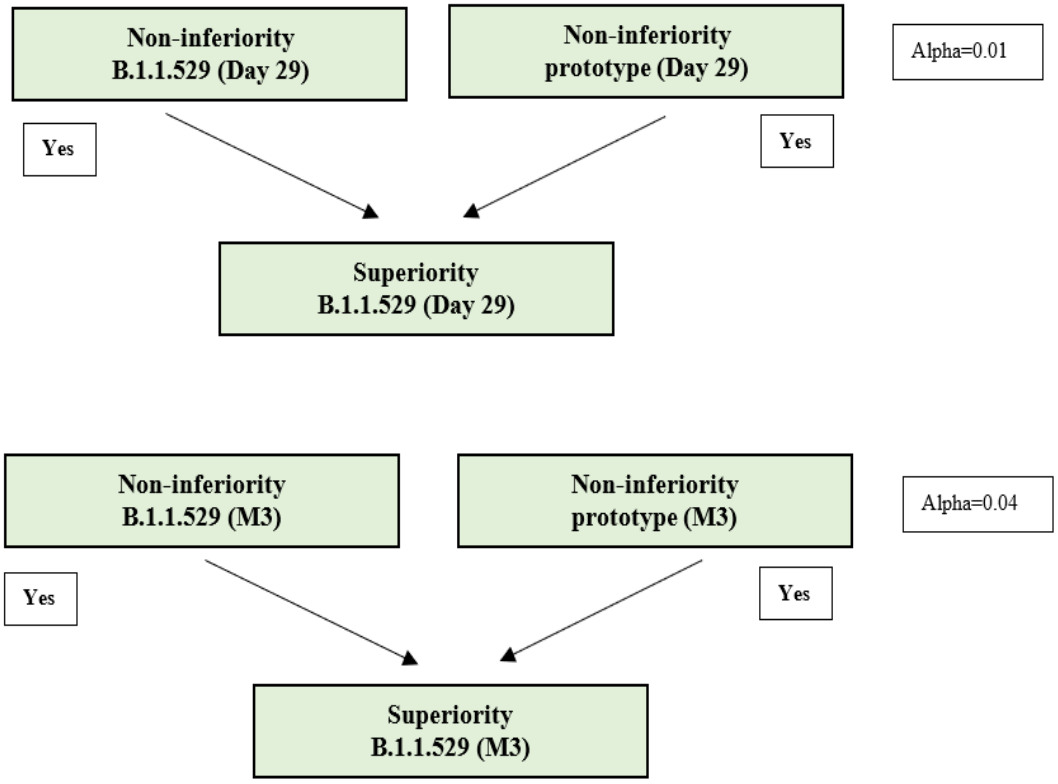
Part 2:

The primary objective on immune response in Part 2 of this study is based on the participants who will receive the 4th dose in Part 2 of the study. There are 6 hypotheses on immune response of mRNA-1273.214 listed below. Part 2 of this study is considered to have met its primary objective if non-inferiority of mRNA-1273.214 against the B.1.1.529 strain, non-inferiority of mRNA-1273.214 against the prototype strain, and superiority of mRNA-1273.214 against the B.1.1.529 strain are demonstrated as compared to mRNA-1273 at any of the following time points post-booster: Day 29, Month 3. The figure below depicts the hypotheses testing strategy.

Primary Hypotheses:

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

Figure: Statistical Hypothesis Testing Strategy of mRNA-1273.214 vs. mRNA-1273 (Part 2)



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

For the primary objective of immune response, hypotheses testing based on participants receiving the 4th dose, alpha of 0.05 (2-sided) will be allocated to the two time points: alpha of 0.01 (2-sided) will be allocated to Day 29, and alpha of 0.04 (2-sided) will be allocated to Month 3.

For the primary immunogenicity objective, the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain and the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the prototype strain at Day 29 will be assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.01. Non-inferiority against the B.1.1.529 strain and the prototype strain are both demonstrated if the lower bound of the 99% confidence interval (CI) of the GMR of mRNA-1273.214 vs. mRNA-1273 against B.1.1.529 is $\geq$ 0.67 (1/1.5) and the lower bound of the 99% CI of the GMR of mRNA-1273.214 vs mRNA-1273 against prototype is $\geq$ 0.67.

Superiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain will be evaluated at Day 29. Once the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against both the B.1.1.529 and the prototype strain at Day 29 is demonstrated,

the 99% CI of GMR (mRNA-1273.214 vs. mRNA-1273) will be used to assess superiority of mRNA-1273.214 as compared to mRNA-1273. If the lower bound of the GMR rules out (>) 1 at Day 29, superiority of mRNA-1273.214 compared to mRNA-1273 against B.1.1.529 will be considered demonstrated.

Hypotheses testing at Month 3 will be performed in the same manner, first testing two non-inferiority hypotheses (one against the B.1.1.529 strain and one against the prototype strain) at alpha of 0.04 level (2-sided). Once non-inferiority is demonstrated for both B.1.1529 and prototype strains, then superiority testing against the B.1.1.529 at alpha of 0.04 level (2-sided) will be performed.

Sample Size Justification:

This study will include:

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

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

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

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

Day 29:

With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at 2-sided alpha of 1.0% at Day 29. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a 2-sided alpha of 1% at Day 29 ranges from CCI. The assumptions are: the true GMT ratio (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

Month 3:

With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at 2-sided alpha of 4.0% at Month 3. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a 2-sided alpha of 4% at Month 3 ranges from CCI. The assumptions are: the true GMT ratio (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5. Specific operating characteristics are presented in the table below.

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

Operating Characteristics for Part 1:

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

Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)
CCI
Key Secondary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)
CCI

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

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

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

Hypotheses testing on immunogenicity data will be performed at 2 timepoints of interest (Day 29 and Month 3 post-booster). To preserve family-wise alpha of 0.05 (2-sided), alpha will be allocated to Day 29 of 0.01 (2-sided) and Month 3 of 0.04 (2-sided).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, 2-sided):

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

prototype is [redacted], the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

Statistical power for hypotheses testing at Month 3 (alpha=0.04, 2-sided):

With approximately CCI evaluable participants in each arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 against the B.1.1.529 strain and against prototype strain at 2-sided alpha of 4.0% at Month 3. With this sample size, there is approximately CCI power to demonstrate superiority of mRNA-1273.214 against the B.1.1.529 variant strain at a 2-sided alpha of 4.0% at Month 3. The assumptions are: the true GMT ratio (mRNA-1273.214 vs. mRNA-1273) against the B.1.1.529 strain ranges from CCI and the true GMT ratio (mRNA-1273.214 vs. mRNA-1273) against the prototype is [redacted], the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

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

The enrollment target of this study is approximately 1328 participants per arm to receive the 4th dose. The Omicron VOC has spread quickly throughout the world as the predominant circulating SARS-CoV-2 strain globally. There may be an urgency to perform Day 29 or Month 3 analysis as early as possible. Depending on the operational feasibility, particularly the testing capability of assays of antibodies against B.1.1.529, the Sponsor may decide to perform the analysis of immunogenicity after immunogenicity data from a subset of the participants receiving the 4th dose becomes available. Such a decision will be documented prior to the planned analysis at Day 29 or Month 3.

The power and operating characteristics for Part 2 under various GMT ratios and 2 different scenarios for the number of evaluable participants with immunogenicity data are provided in the table below. Based on CCI evaluable participants per arm (4th dose), under the same assumptions outlined above, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 compared to mRNA-1273 against the- B.1.1.529 at Day 29 at $\alpha = 1\%$ if true GMT ratio CCI; and there is approximately CCI power to demonstrate superiority at $\alpha = 1\%$ if the true ratio if CCI With this size, there is CCI power at Month 3 (primary objective) at $\alpha = 4\%$ (2-sided) if the true GMT ratio is CCI; and there is CCI power to demonstrate superiority at $\alpha = 4\%$ (2-sided) if the true GMR is CCI.

Operating Characteristics for Part 2:

True GMR (mRNA-1273.214 vs. mRNA-1273 against B.1.1.529)	Number evaluable patients per arm (4th dose)	Minimum empirical GMR for the primary objective	Power
Two-sided Type I Error (α) = 0.01 (Day 29)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			
Two-sided Type I Error (α) = 0.04 (Month 3)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			

Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)

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

Analysis Populations (Part 1 and Part 2):

Set	Description
Full Analysis Set (FAS)	The FAS consists of all randomized participants who receive the IP. Participants will be analyzed according to their randomized study arm.
Modified Intent-to-Treat (mITT) Set	The mITT Set consists of all participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) prebooster, ie, all FAS participants with pre-booster/baseline SARS-CoV-2 negative status. Participants will be analyzed according to their randomized study arm.
PP Set for Immunogenicity (PPSI)	The PPSI consists of all participants in the FAS who receive 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.
PP Set for Immunogenicity – SARS-CoV-2 negative (PPSI-Neg)	Participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection up to day of visit analysis, ie, who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid. PPSI-Neg will be the primary analysis set for analyses of immunogenicity unless otherwise specified.
Solicited Safety Set	The Solicited Safety Set consists of all randomized participants who receive IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the study arm that they actually received.
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.
PP Set for Efficacy (PPSE)	The PPSE consists of all participants in the mITT who receive the planned study vaccination and have no major protocol deviations that impact key or critical data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PP = Per protocol; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Immunogenicity Analysis:

Part 1: mRNA-1273.529 vs. mRNA-1273

The primary objective on immune response in Part 1 of this study is based on the participants who will receive the 4th dose in the study. There is 1 hypothesis on immune response of mRNA-1273.529. Part 1 is considered to meet its primary objective if non-inferiority of mRNA-1273.529 against the B.1.1.529 strain is demonstrated as compared to mRNA-1273 (primary hypothesis).

An analysis of covariance (ANCOVA) model will be performed to assess the difference in immune response between mRNA-1273.529 and mRNA-1273 as the 4th dose in the subgroup of participants who received the 4th dose. This analysis will be carried out for immune response against the B.1.1.529 strain and the prototype virus strain separately in the PPSI-Neg analysis population.

Specifically, for immune response against the B.1.1.529 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.529 and mRNA-1273) will be the fixed effect, adjusting for age groups (< 65, ≥ 65 years) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the geometric least square mean (GLSM) from the model and its corresponding 99% CIs will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.529 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 99% CIs will be provided. The 99% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for mRNA-1273.529 at Day 29 compared to the mRNA-1273 as a booster for non-inferiority testing.

Against the B.1.1.529 strain, the non-inferiority of immune response of mRNA-1273.529 as compared to mRNA-1273 will be considered demonstrated if the lower bound of the corresponding 99% CI is ≥ 0.67 (Day 29) based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 is demonstrated, superiority of mRNA-1273.529 as compared to mRNA-1273 against B.1.1529 will be tested; if the lower bound of the 99% CI of the GMT ratio is > 1 (Day 29), superiority is demonstrated.

The same ANCOVA model will be used to assess immune response of mRNA-1273.529 against the B.1.1.529 strain at Month 3; 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority and superiority. For the immune response against the prototype virus strain, the same analysis method will be used.

Part 2: mRNA-1273.214 vs. mRNA-1273

The primary objective on immune response in Part 2 of this study is based on the participants who will receive the 4th dose in Part 2 of the study. There are 6 hypotheses on the immune response of mRNA-1273.214 (see figure above). Part 2 is considered to meet its primary objective if non-inferiority of mRNA-1273.214 against the B.1.1.529 strain, non-inferiority of mRNA-1273.214 against the prototype, and superiority of mRNA-1273.214 against the B.1.1.529 strain are demonstrated as compared to mRNA-1273 at any of the following time points post-booster: Day 29, Month 3.

An ANCOVA model will be carried out to assess the difference in immune response between mRNA-1273.214 and mRNA-1273 in the subgroup of participants who received the 4th dose. This analysis will be carried out for the immune response against the B.1.1.529 strain and the prototype virus strain separately using the PPSI-Neg analysis population.

Specifically, for immune response against the B.1.1.529 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.214 and mRNA-1273) will be the fixed effect, adjusting for age groups (< 65, ≥ 65 years) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the geometric least square mean (GLSM) from the model and its corresponding 99% CIs will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.214 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 99% CIs will be provided. The 99% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for mRNA-1273.529 at Day 29 compared to the mRNA-1273 as a booster for non-inferiority testing.

Against the B.1.1.529 strain, the non-inferiority of immune response of mRNA-1273.214 as compared to mRNA-1273 will be considered demonstrated if the lower bound of the corresponding 99% CI is ≥ 0.67 based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 is demonstrated, superiority of mRNA-1273.214 as compared to mRNA-1273 against B.1.1529 will be tested (at Day 29); if the lower bound of the 99% CI of the GMT ratio is > 1, superiority is demonstrated.

The same ANCOVA model will be used to assess immune response of mRNA-1273.214 against the B.1.1.529 strain at Month 3; 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority and superiority. For the immune response against the prototype virus strain, the same analysis method will be used.

As part of the secondary analysis to assess for immune response against other variants, the same analysis method described above will be used. A 95% CI for GMR will be used to assess for non-inferiority and superiority.

The following section is applicable to both Part 1 and Part 2:

Immunogenicity, SARS-CoV-2-specific bAb and nAb, will be assessed at multiple timepoints in this study. Mixed effects models will be used to analyze all post-booster/baseline measures. The models will include treatment group, analysis visit, treatment by visit interaction, and adjustment for age groups and pre-booster titer levels. 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 (ratio of GMTs) for mRNA-1273.529 and for mRNA-1273.214 with respect to mRNA-1273 will be estimated from each model and the corresponding 95% CI will be provided at each post-boost time point.

For each of the antibodies of interest (eg, levels of SARS-CoV-2–specific bAb and SARSCoV-2-specific nAb), the GMT or level with corresponding 95% CI at each time point, and GMFR of post-booster/pre-booster titers or levels with corresponding 95% CI at each post baseline time point will be provided for each arm. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: number of participants (n), median, minimum, and maximum. PPSI will be used as the analysis population to summarize the immune responses (antibodies of interest) and the above summary statistics including GMT and GMFR will be provided by pre-booster/study baseline SARS-CoV-2 status.

SRR definitions and analyses will be defined in the SAP.

Planned Analyses

The planned analyses of immunogenicity and safety will be conducted after participants have completed Day 29 and Month 3 visit assessments. Analyses of the Month 6 and Month 12 visit including the Phase B (open-label, observational) part of the study will be exploratory.

The final analysis of all endpoints will be performed after all participants have completed or discontinued from the study. Results of this analysis will be presented in a final CSR.

Efficacy Analyses:

Number and incidence rates of symptomatic COVID-19 disease, asymptomatic SARS-CoV-2 infection, as well as COVID-19 regardless of symptoms will be provided for each study arm. Vaccine efficacy may be estimated if the number of cases accrued is deemed to be sufficient.

Efficacy analyses will be performed using the mITT and PP Set for Efficacy analysis populations. The details will be provided in SAP.

Safety Analyses:

All safety analyses will be based on the Safety Set, except analyses of solicited ARs, which will be based on the Solicited Safety Set.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic ARs), unsolicited AEs, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after vaccination, and with Grade 3 or higher solicited AR will be provided. A 2-sided 95% exact CI using the Clopper Pearson method will be provided for the percentage of participants with any solicited AR.

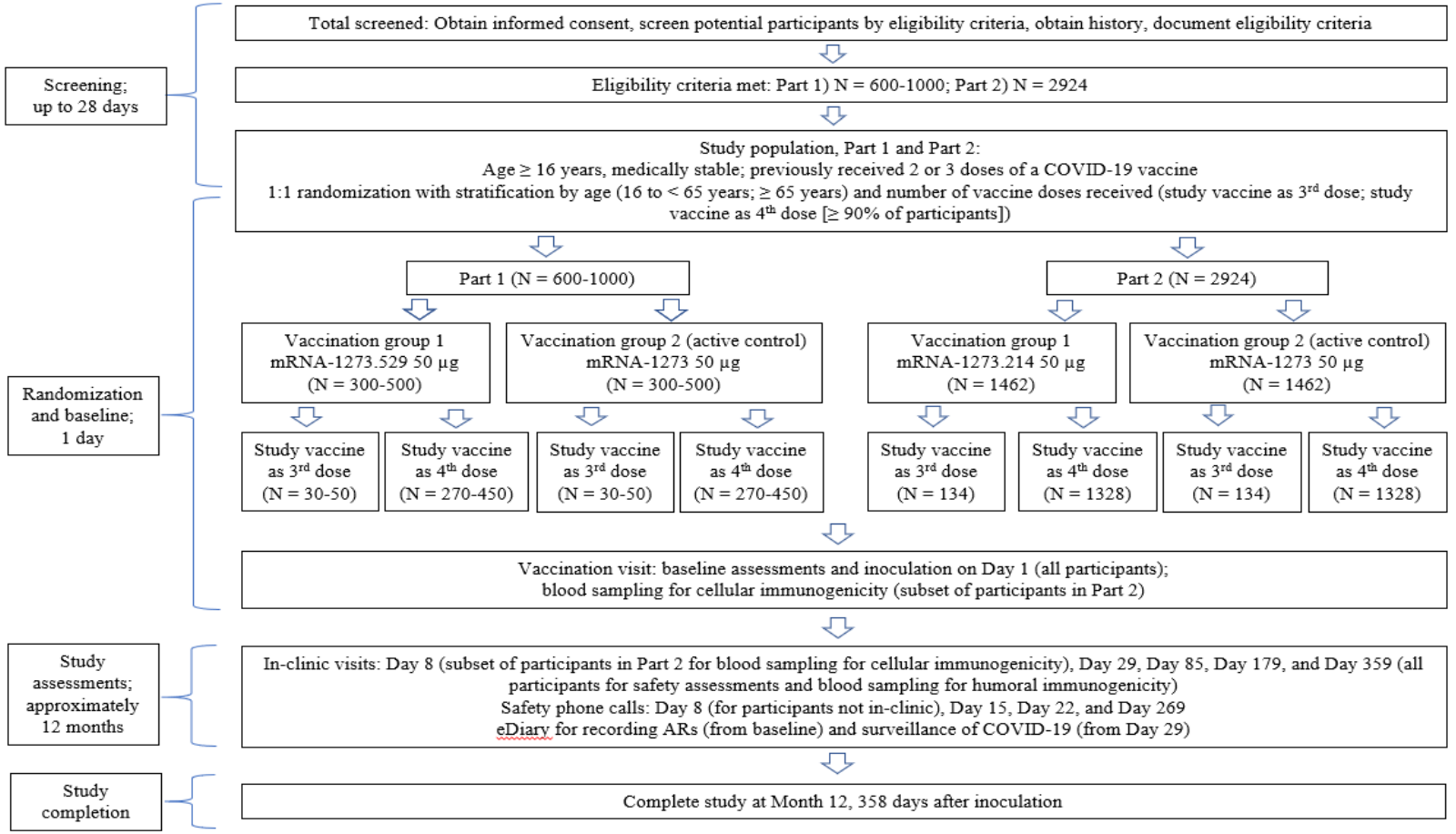
The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be summarized. Unsolicited AEs will be presented by MedDRA system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

Pregnancy outcomes will also be summarized.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: COVID-19 = coronavirus disease 2019; mRNA = messenger ribonucleic acid; N = number.

1.3. Schedule of Events

Table 1: Schedule of Events Part 1

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
ICF, demographics, concomitant medications, medical history[2]	X										
Confirm participant meets inclusion and exclusion criteria	X	X									
Physical examination[3]	X	X				X	X	X		X	X
Vital signs[4]	X	X									X
Pregnancy testing[5]	X	X									
Randomization		X									
Dosing											
Study injection (including 15-minute post-dosing observation period)		X									
Surveillance for COVID-19											

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

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

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

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

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

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.
3. Physical examination: a full physical examination, including vital signs, height, and weight, will be performed at Screening and Day 1. Body mass index will be calculated at the Screening Visit only. Symptom-directed physical examinations will be performed on Day 29, Day 85, Day 179, D359/EoS, and during USV visits. On the day of the vaccination, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as a MAAE.
4. Vital signs measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 15 minutes after vaccination. When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before dosing must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination. A pulse oximeter measurement may be performed at the unscheduled visit, if applicable/available.

5. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating hormone level should be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.
6. An unscheduled visit may be prompted by reactogenicity issues, illness visit for COVID-19, or new or ongoing AEs. If a participant experiences symptoms suggestive of COVID-19, the participant will be directed as soon as possible and within 24 hours to undergo testing as outlined in Section 8.9.2. An unscheduled study illness visit will be arranged as soon as possible and within 72 hours for participants who test positive for SARS-CoV-2 as per testing as outlined in Section 8.9.2. At this visit, an NP swab will be collected to evaluate for the presence of SARS-CoV-2 infection. If a study site visit is not possible, a home visit may be arranged to collect a swab sample and conduct clinical evaluations. Additionally, clinical information will be collected to evaluate the severity of the clinical case.
7. Samples for humoral immunogenicity must be collected prior to receipt of vaccination on Day 1. All participants will have blood drawn for humoral immunogenicity.
8. The participant will record data in the eDiary approximately 15 minutes after dosing while at the study site, with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of dosing, and for 6 days following. Any solicited AR that is ongoing beyond Day 7 will be reported verbally by participants at the scheduled Safety Calls, until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. Participants will be given thermometers to record their body temperatures and rulers to measure any injection site reactions.
9. Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations.
10. All concomitant medications and non-study vaccinations will be recorded through 28 days after vaccination, except authorized or investigational COVID-19 vaccine(s) given at any time during the study period should be recorded (Day 29 through EoS).

Table 2: Schedule of Events Part 2

Visit Number		1	2			3	4	5		6	USV
Type of Visit	C	C	C/SC	SC	SC	C	C	C	SC	C	C
Month Timepoint		M0				M1	M3	M6	M9	M12	Up to M12
Study Visit Day	Screening[1]	D1 (Baseline)	D8	D15	D22	D29	D85	D179	D269	D359/EoS	USV
Window Allowance (Days)	-28		+3	+3	+3	-3/+7	±7	±14	±7	±14	N/A
Days Since Vaccination	-	0	7	14	21	28	84	178	268	358	
ICF, demographics, concomitant medications, medical history[2]	X										
Confirm participant meets inclusion and exclusion criteria	X	X									
Physical examination[3]	X	X	X			X	X	X		X	X
Vital signs[4]	X	X									X
Pregnancy testing[5]	X	X									
Randomization		X									
Dosing											
Study injection (including 15-minute post-dosing observation period)		X									

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

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

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

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

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

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.
3. Physical examination: a full physical examination, including vital signs, height, and weight, will be performed at Screening and Day 1. Body mass index will be calculated at the Screening Visit only. Symptom-directed physical examinations will be performed on Day 8 (if applicable), Day 29, Day 85, Day 179, D359/EoS, and during USV visits. On the day of the vaccination, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during a study visit should be reported as a MAAE.

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

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LIST OF ABBREVIATIONS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
cMRI	cardiac magnetic resonance imaging
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
ECG or EKG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio

Abbreviation or Specialist Term	Definition
GMT	geometric mean titer
HCP	healthcare practitioner
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IP	investigational product
IRT	interactive response technology
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NHS	National Health Service
NP	nasopharyngeal
PP	per protocol
PPE	personal protective equipment
PPSE	per protocol set for efficacy
PPSI	per protocol set for immunogenicity
PPSI-neg	per protocol set for immunogenicity –SARS-CoV-2 negative
QA	quality assurance
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
S	spike

Abbreviation or Specialist Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoE	schedule of events
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia
USV	unscheduled safety visit
VOC	variants of concern
WHO	World Health Organization
WOCBP	women of childbearing potential

2. INTRODUCTION

2.1. Study Rationale

There is an urgent need for vaccination strategies that induce broader protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOC), including the Omicron variant, to decrease morbidity and mortality. In addition, it is currently not known whether breakthrough infections could occur long term due to waning antibody titers (Doria-Rose et al 2021, Pegu et al 2021). Based on the experience of mRNA-1273, available under Emergency Use Authorization (EUA), and leveraging the flexible nature of the messenger ribonucleic acid (mRNA) technology, ModernaTX, Inc (the Sponsor) is evaluating mRNA vaccines to address the Omicron variant.

2.2. Background and Overview

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome and severe acute respiratory syndrome (SARS). An outbreak of a novel coronavirus (later designated SARS-CoV-2) initially emerged in Wuhan, Hubei Province, China in December 2019. The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on 11 Mar 2020 with nearly 265 million confirmed cases and 5.2 million deaths by 05 December 2021 (WHO 2021).

The Sponsor's scalable mRNA/lipid nanoparticle (LNP) technology platform allowed for a rapid response to the pandemic and was used to develop mRNA-1273, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA (CX-024414) that encodes for the full-length SARS-CoV-2 spike (S) protein of the Wuhan-Hu-1 SARS-CoV-2 virus, modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the S protein into a prefusion conformation. In December 2020, mRNA-1273 was granted EUA for the prevention of COVID-19 in individuals 18 years of age and older based on the demonstration of efficacy and safety in a Phase 3 pivotal trial conducted in persons at high risk for SARS-CoV-2 infection (Baden et al 2021). On January 31, 2022, the FDA announced the approval of mRNA-1273 marketed as Spikevax (FDA News Release 2022).

Over the course of the pandemic, SARS-CoV-2 variants have emerged and are likely to continue to emerge, some of which may prove to have some level of escape from immunity associated with previous infection or vaccination. Recently, newer variants have raised concern, due to reports of increased infectivity or reduction in the ability of convalescent sera or sera from vaccinated subjects to neutralize these emergent strain variants. Mutations occurring in the receptor-binding domain (RBD) are of particular concern, as this site includes the dominant neutralization epitopes on the S protein and these mutations could impact the effectiveness of antibodies elicited by infection or vaccination in neutralizing the virus (Greaney et al 2021).

These recent evolutionary events indicate that SARS-CoV-2 has the capacity to develop more efficient transmission between human hosts (Martin et al 2021) and vaccination strategies to control the virus need to be responsive to this evolution. A SARS-CoV-2 variant, Alpha (B.1.1.7), rapidly spread from southeast England around the globe. The Beta (B.1.351) variant emerged in South Africa, and the Gamma (P.1 lineage) variant was initially reported in Brazil. The Delta (B.1.617.2) variant, which contains 2 mutations in the RBD (L452R and T478K), circulated globally in 2021. In vitro characterization of sera from individuals recently vaccinated with the 2-dose regimen of the Moderna COVID-19 vaccine at the 100 µg dose showed that the Moderna COVID-19 vaccine produced neutralizing titers against key emerging variants tested, including Alpha, Beta, and Delta (Wang et al 2021, Wu et al 2021, Choi et al 2021). The studies showed no significant reduction in neutralizing titers against the Alpha variant relative to the prototype Wuhan-Hu-1 strain and a 2.1-fold reduction versus the Delta variant; however, a greater than 6-fold reduction in neutralizing titers was observed against the Beta variant relative to the Wuhan-Hu-1. Evidence from adenovirus vector SARS-CoV-2 vaccines based on the Wuhan-Hu-1 sequence suggests reduced vaccine efficacy against moderate to severe COVID-19 in South Africa where the Beta variant circulated (Madhi et al 2021, Sadoff et al 2021). A real-world effectiveness study that the Sponsor conducted with Kaiser Permanente found that vaccine effectiveness against the Delta variant declined from 94.1% 14-60 days after vaccination to 80.0% 151-180 days after vaccination (Bruxvoort et al 2021).

In November 2021, the SARS-CoV-2 Omicron variant (B.1.1.529) was detected in South Africa and epidemiological information about its spread in other regions is being evaluated. Available evidence suggests that the Omicron variant has transmission advantage over prior variants. The Omicron variant has significant antigenic change with a potential growth advantage. In addition, it contains potential antibody escape site mutations (such as K417N, T478K, E484A, N501Y). Results from the Sponsor show that 1 month after completing the primary series, mRNA-1273-elicited serum neutralization of Omicron variant pseudovirus was not detectable. However, neutralization was observed at 2 weeks after an mRNA-1273 booster dose, although activity was reduced relative to the prototype D614G strain and remained lower than that observed against the prototype D614G strain at 1 month after the primary series. Further evaluation of the in vitro neutralization of the Omicron variant, using sera from vaccinees, is currently in progress.

Overall, this study will assess whether a single booster dose of the mRNA vaccine boosts antibody responses to the Omicron variant and the prototype strain. Participants who previously received 2 or 3 doses of a COVID-19 vaccine will receive a single booster dose of the mRNA-1273.529, mRNA-1273.214, or mRNA-1273 vaccines in this study.

2.2.1. mRNA-1273, mRNA-1273.529, and mRNA-1273.214

The Sponsor has developed a rapid response, proprietary vaccine platform based on a 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.

mRNA-1273

mRNA-1273 encodes for the full-length S protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-2P in a prefusion conformation. The CoV-S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAbs) that prevent infection (Corbett et al 2020). It has been confirmed that the stabilized SARS-CoV-2 S2P antigen presents in the correct prefusion conformation (Wrapp et al 2020).

In December 2020, mRNA-1273 was granted EUA for the prevention of COVID-19 for individuals 18 years of age and older. It is currently being evaluated for safety, immunogenicity, and efficacy in ongoing Phase 1 (NCT04283461), Phase 2 (NCT04405076), and Phase 3 (NCT04470427) trials. All 3 trials have been modified to allow for unblinding and crossover of placebo subjects and/or to assess safety and immunogenicity of booster doses of vaccine.

mRNA-1273.529

Developed similarly to mRNA-1273 on the Sponsor's platform, mRNA-1273.529 contains mRNA CX-031302 encoding for the S-2P of B.1.1.529.

mRNA-1273.214

mRNA-1273.214 contains CX-024414, the mRNA that encodes for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2 and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant.

2.2.2. Nonclinical Studies

Nonclinical study data for mRNA-1273 is available in the Investigator's Brochure (IB). Nonclinical studies of mRNA-1273.529 and mRNA-1273.214 are ongoing.

2.2.3. Clinical Studies

Clinical study data for mRNA-1273 is available in the IB. mRNA-1273.529 and mRNA-1273.214 are also being evaluated in the Sponsor's trial, mRNA-1273-P205, a Phase 2/3, open-label study to evaluate the immunogenicity and safety of boosters for SARS-CoV-2 variants. Data from the Sponsor's Phase 2 trials suggest that mRNA-1273.211, a bivalent vaccine that

contains mRNA encoding for the S-2P of Wuhan-Hu-1 and mRNA encoding for the S-2P of B.1.351 at a 1:1 ratio, induced numerically similar or higher and more durable neutralizing responses against both vaccine-matched and unmatched strains compared to the monovalent mRNA-1273 and mRNA-1273.351 (encodes for S-2P of B.1.351) vaccine. This supports the hypothesis that the bivalent mRNA-1273.214 vaccine to be tested in this study may generate more durable neutralizing responses against the Omicron variant strain and the prototype strain compared to mRNA-1273.

2.3. Benefit/Risk Assessment

2.3.1. Known Potential Benefits

The following benefits may accrue to participants that will receive the mRNA-1273.529, mRNA-1273.214, or mRNA-1273 booster vaccines:

- The mRNA-1273.529, mRNA-1273.214, or mRNA-1273 vaccine as a booster dose may provide improved protection against COVID-19 VOC.
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection and ongoing surveillance for COVID-19 throughout the study.
- The study will contribute to the development of a vaccine against COVID-19 VOC, a current pandemic disease.

2.3.2. Risks from Study Participation and Their Mitigation

The safety profile of mRNA-1273 is largely based on data from the pivotal Phase 3 study (Study mRNA-1273-P301). It is expected that the safety profile of mRNA-1273.529 and mRNA-1273.214 will be similar to mRNA-1273.

Solicited adverse reactions (ARs) were reported more frequently among vaccine participants than among placebo participants. The most frequently reported ARs after any dose in the vaccine group were pain at the injection site, fatigue, headache, myalgia, and chills. The most common solicited local AR was pain. Solicited systemic ARs were reported more frequently by vaccine participants after dose 2 (fatigue, 65.3%, headache, 58.6%, myalgia, 58% and arthralgia, 42.8%) than after dose 1 (fatigue, 37.2%, headache, 32.7%, myalgia, 22.7% and arthralgia,16.6%). Grade 3 systemic ARs were also reported more frequently after dose 2 than after dose 1. The majority of local and systemic ARs had a median duration of 1 to 3 days.

Overall, there was a higher reported rate of some ARs in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above.

Grade 3 solicited local ARs were more frequently reported after dose 2 than after dose 1.

Unsolicited adverse events (AEs) that occurred within 28 days following each vaccination were reported by 23.9% of participants who received mRNA-1273 and 21.6% of participants who received placebo. Unsolicited AEs that occurred in ≥ 1% of study participants who received mRNA-1273 and at a rate at least 1.5-fold higher rate than placebo, were lymphadenopathy related events (1.1% vs. 0.6%). All of the lymphadenopathy events are similar to the axillary swelling/tenderness in the injected arm reported as solicited ARs. Several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritus. Consultation with a dermatopathologist suggested that these were most likely dermal hypersensitivity and were unlikely to represent a long-term safety concern.

Hypersensitivity AEs were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. There have been no cases of severe hypersensitivity or anaphylactic reactions reported immediately after vaccination in the trial to date.

There were 3 reports of Bell's palsy in the mRNA-1273 vaccine group (one of which was a serious AE [SAE]), which occurred 22, 28, and 32 days after vaccination, and 1 in the placebo group which occurred 17 days after vaccination. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine.

SAEs were reported at the same rates in participants who received mRNA-1273 and placebo from the first dose until the last observation. There were 2 SAEs of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination. There was 1 SAE of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination.

There were no other notable patterns or numerical imbalances between study arms for specific categories of AEs (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

In the post-authorization period, there have been very rare reports of anaphylaxis following mRNA-1273 administration. In addition, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young 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. Safety will be monitored throughout the study.

2.3.3. Overall Benefit/Risk Conclusion

The evolving antigenic variation of SARS-CoV-2 underscores the urgent need for vaccination strategies that induce broader protection, specifically against VOC with attendant risk of viral escape. The Sponsor is developing monovalent and multivalent mRNA vaccines (mRNA-1273.529 and others) that are similar to the mRNA-1273 vaccine, but in which the mRNA encodes for mutations included in the S protein of both the prototype strain (Wuhan-Hu-1) and VOC. It is not yet known the degree to which currently available authorized/approved mRNA-1273 vaccine and variant-targeted mRNA-1273 vaccines are protective against new variants.

Considering the safety data for mRNA-1273 to date and the similarities of mRNA-1273 to mRNA-1273.529 and mRNA-1273.214, the Sponsor considers the potential benefits of participation in this study to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective in Part 1 and Part 2 are provided in Table 3 and Table 4, respectively.

Table 3: Study Objectives and Endpoints for Part 1 (mRNA-1273.529 and mRNA-1273)

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• Geometric mean titer (GMT) of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration
To evaluate the safety and reactogenicity of mRNA-1273.529 and mRNA-1273 administered as a booster dose	• Solicited local and systemic reactogenicity ARs during a 7-day follow up period after vaccination • Unsolicited AEs during the 28-day follow-up period after vaccination • SAEs, medically attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (AESIs) from Day 1 to end of study
Secondary	
Key Secondary	
To demonstrate superiority of the immune response of mRNA-1273.529 compared to mRNA-1273 administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• GMT of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 and Month 3 after study vaccine administration

Other Secondary	
To demonstrate non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against both the B.1.1.529 and the prototype strain at all evaluable time points	• GMT of mRNA-1273.529 and mRNA-1273 against both the B.1.1.529 and the prototype strain at all evaluable time points after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against both the B.1.1.529 and the prototype strain at all evaluable time points after study vaccine administration
To evaluate the seroresponse rate (SRR) of mRNA-1273.529 and mRNA-1273 boosters administered as a 4th dose	• SRR against the B.1.1.529 strain • SRR against the prototype strain
Exploratory Objectives	
To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.529 booster or mRNA-1273 booster	Reverse transcriptase polymerase-chain reaction (RT-PCR)-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants based on the following criteria: • Protocol-defined COVID-19 case definition o The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND o The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. • Center for Disease Control (CDC)-defined COVID-19 definition based on the CDC criteria: the presence of one of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample • Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment

To evaluate the immunogenicity of mRNA-1273.529 booster against other variant strains	• GMT of mRNA-1273.529 against other variant strains (eg, Alpha, Beta, Delta) after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against other variant strains after study vaccine administration • GMFR of mRNA-1273.529 against other variant strains after study vaccine administration • SRR against other variant strains
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; GMFR = geometric mean fold rise; GMR = geometric mean titer ratio; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

Table 4: Study Objectives and Endpoints for Part 2 (mRNA-1273.214 and mRNA-1273)

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• Geometric mean titer (GMT) of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration
To demonstrate non-inferiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the prototype strain at Day 29 or Month 3	• Geometric mean titer (GMT) of mRNA-1273.214 and mRNA-1273 against the prototype strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Day 29 or Month 3 after study vaccine administration
To demonstrate superiority of the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain at Day 29 or Month 3	• GMT of mRNA-1273.529 and mRNA-1273 against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.529}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Day 29 or Month 3 after study vaccine administration
To evaluate the safety and reactogenicity of mRNA-1273.214 and mRNA-1273 administered as a booster dose	• Solicited local and systemic reactogenicity ARs during a 7-day follow up period after vaccination • Unsolicited AEs during the 28-day follow-up period after vaccination • SAEs, medically attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (AESIs) from Day 1 to end of study
Secondary	
To evaluate the seroresponse rate (SRR) of mRNA-1273.214 and mRNA-1273 boosters administered as a 4th dose	• SRR against the B.1.1.529 strain • SRR against the prototype strain
To evaluate the immune response of mRNA-1273.214 compared to mRNA-1273 booster administered as a 4th dose against other variant strains at Day 29 or Month 3	• GMT of mRNA-1273.214 and mRNA-1273 against other variant strains at Day 29 or Month 3 • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against other variant strains at Day 29 or Month 3 • SRR against other variant strains

To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273.214 booster or mRNA-1273 booster	Reverse transcriptase polymerase-chain reaction (RT-PCR)-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants based on the following criteria:
	• Protocol-defined COVID-19 case definition
	  o The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
	  o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
	  o The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
	• Center for Disease Control (CDC) defined COVID-19 definition based on the CDC criteria: the presence of one of the CDC listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample
	• Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment

Exploratory Objectives	
To evaluate cellular immunogenicity in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of T-cells and B-cells after vaccination
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates

To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a 4th dose study vaccine in participants at Month 6	• GMT of mRNA-1273.214 against both the B.1.1.529 and the prototype strain at Month 6 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the B.1.1.529 strain at Month 6 after study vaccine administration • Ratio of $GMT_{mRNA\text{-}1273.214}/GMT_{mRNA\text{-}1273}$ against the prototype strain at Month 6 after study vaccine administration • GMFR of mRNA-1273.214 and mRNA-1273 against the B.1.1.529 and prototype strain at all evaluable timepoints after study vaccine administration • SRR against both the B.1.1.529 and prototype strain at Month 6

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; GMFR = geometric mean fold rise; GMR = geometric mean titer ratio; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

4. STUDY DESIGN

4.1. General Design

The study is a Phase 2/3, 2-part, randomized, observer-blind, active-controlled, multicenter study to evaluate the immunogenicity and safety of mRNA-1273.529 and mRNA-1273.214 booster vaccine in medically stable individuals 16 years and older. The mRNA-1273.529 vaccine to be tested in this study contain mRNAs encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). The mRNA-1273.214 vaccine contains the Wuhan Hu-1 and B.1.1.529 mRNAs (2 mRNAs: CX024414 encoding for the S-2P of Wuhan Hu-1 and CX-031302 encoding for the S-2P of B.1.1.529) and formulated in the same LNP.

The study consists of 2 parts with 2 phases each:

In **Part 1**, approximately 600-1000 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.529 or 50 µg of mRNA-1273 (active control. Randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least ≥ 90% of participants will receive study vaccine as the 4th dose. The potential number of participants in each arm and the randomization ratio can be found in Table 5.

In **Part 2**, approximately 2,924 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.214 or 50 µg of mRNA-1273 (active control). Randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least ≥ 90% of participants will receive study vaccine as the 4th dose. The potential number of participants in each arm and the randomization ratio can be found in Table 6.

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

Table 5: Part 1 Study Arm and Dose Levels

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

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

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

Table 6: Part 2 Study Arm and Dose Levels

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

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

All participants will have previously received 2 or 3 doses of an authorized/approved COVID-19 vaccine. Participants who had previously received 2 doses of a COVID-19 vaccine as a primary series will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the third dose, and participants who have previously received a primary series and 1 booster dose will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the 4th dose. Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine as the 3rd dose of a COVID-19 vaccine. Participants who will receive the 3rd dose as part of the study may have previously received 2 doses of a mRNA or a non-mRNA COVID-19 vaccine (a mixed approach is acceptable).

Medically stable individuals, ages 16 and above (to include 2 age groups: 16 to < 65 and ≥ 65 years) 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 10 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 polymerase chain reaction (PCR) within 90 days prior to enrollment will be 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 (up to 28 days before the Day 1 visit), Vaccination Visit at Day 1 and subsequent study visits on Day 8 (for a subset of participants in Part 2), Day 29 (Month 1), Day 85 (Month 3), Day 179 (Month 6), and

Day 359 (Month 12), with up to 13 months of study participation. Unscheduled visits for potential symptoms of COVID-19 will include PCR testing.

4.2. Scientific Rationale for Study Design

This 2-phase study includes a randomized, blinded phase (Phase A) and an open-label, observational phase (Phase B). Phase A is designed as a 2-part, randomized, stratified, observer-blind, active-controlled study to demonstrate the immunogenicity and safety of the mRNA-1273.529 and mRNA-1273.214 vaccine in medically stable individuals 16 years and older. Participants will receive a single dose of either mRNA-1273.529/mRNA-1273.214 or mRNA-1273 (active comparator) booster vaccine as the 3rd or 4th dose of a COVID-19 vaccine.

Because it is possible that participants are exposed to SARS-CoV-2 through community exposure, NP swab samples and the serologic assays will be collected before vaccination on Day 1 to help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed. Furthermore, NP swab specimen(s) for assessment of pathogens including SARS-CoV-2, will also be collected at any time during the study period if participants have symptoms suggestive of COVID-19 or other upper or lower respiratory infection at the investigator's discretion. Additionally, clinical information will be collected to evaluate the severity of the clinical case.

Following authorization of the mRNA-1273.214 booster, the study was amended to allow a transition to Phase B, the open-label, observational phase. Transitioning the study to the open-label, observational phase allows eligible participants in either treatment arm in Part 1 and Part 2 to receive an additional booster outside of the study after completing the Month 6 and Month 3 study visit, respectively.

4.3. Justification for Dose and Control Product

The Sponsor developed mRNA-1273, an mRNA-based vaccine against SARS-CoV-2. Having achieved the primary endpoint in a pivotal Phase 3 study conducted in persons at high risk for SARS-CoV-2 infection in December 2020, mRNA-1273 was granted EUA for the prevention of COVID-19 for individuals 18 years of age and older based on the demonstration of efficacy and safety in a pivotal Phase 3 study (Baden et al 2021). Given the potential for waning immunity, the emergence of highly transmissible SARS-CoV-2 variants, and the ability of some variants to partially escape immunity, the Sponsor assessed the immunogenicity and safety of a 50 µg booster immunization. Administration of a booster dose of 50 µg at least 6 months after administration of the second of 2 doses of the mRNA-1273 primary series greatly enhanced immune responses compared to pre-boost levels. Additionally, no new safety signals emerged upon administration of the 50 µg booster dose (Phase 2 mRNA-1273-P201; NCT04405076). Based on cumulative evidence, the benefit-risk profile of a 50 µg booster dose of mRNA-1273 is

favorable, particularly in light of increasing breakthrough disease with the emergence of the Delta/Omicron variants. The FDA has authorized the emergency use administration of a single booster dose (50 µg) of mRNA-1273 vaccine at least 5 months after completing the primary series of this vaccine in individuals 18 years of age and older.

Based on the Sponsor's prior studies as described above with mRNA-1273, a dose level of 50 µg for mRNA-1273.529 and mRNA-1273.214 was selected and is anticipated to be immunogenic and well tolerated.

4.4. End of Study Definition

The end of study (EoS) is defined as completion of the last visit of the last participant in each part of the study or last scheduled procedure as shown in the schedule of events (SoE) Table 1 for Part 1 and Table 2 for Part 2) for the last participant in the study.

A participant is considered to have completed the study only if they complete the final visit on Day 359 (Month 12) as shown in the SoE (Table 1 and Table 2).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Is male or female, at least 16 years of age at the time of consent (Screening Visit).
2. Investigator's assessment that the participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized (Section 11.2). A Follicle stimulating hormone (FSH) level should be measured at the discretion of the investigator to confirm postmenopausal status, if necessary.
5. 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.
6. Has received 2 prior doses of one of the following approved/authorized COVID-19 vaccines: Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, Janssen. A heterologous vaccine regimen is acceptable.
7. Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine (Moderna or Pfizer/BioNTech) as the 3rd dose of a COVID-19 vaccine. Participants who will receive the 3rd dose as part of the study may have previously received 2 doses of an approved/authorized mRNA or a non-mRNA COVID-19 vaccine (a heterologous vaccine regimen is acceptable).

5.2. Exclusion Criteria

Participants meeting any of the following criteria, unless noted otherwise, will be excluded from the study:

1. Had close contact (without personal protective equipment [PPE]) as defined by the CDC in the past 14 days to someone diagnosed with SARS-CoV-2 infection or COVID-19 within 10 days of the close contact. 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 by 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 received a total of 4 doses or more of COVID-19 vaccine.
6. Has received a COVID-19 vaccine at a dose different from the authorized/approved dose.
7. 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.
8. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease requiring immunosuppressive treatment or other immunosuppressive condition.
9. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
10. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any components of mRNA vaccine.
11. Reported history of bleeding disorder that is considered a contraindication to intramuscular (IM) injection or phlebotomy.
12. 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.

13. 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 or equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.
14. Has received or plans to receive any licensed vaccine ≤ 28 days prior to the study injection (Day 1) or plans to receive a licensed vaccine within 28 days after the study injection (with the exception that approved seasonal influenza vaccine may be received by at least 7 days and preferably 14 days apart from the study injection).
15. Has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive during the study.
16. Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer).
17. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
18. 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.
19. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

5.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment. 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 date of informed consent, demography, screen failure details, eligibility criteria, and information on any SAE which may have occurred from the time informed consent was obtained to the time of withdrawal.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time if they will be eligible upon rescreening.

6. STUDY TREATMENT

6.1. Investigational Product and Active Comparator Administered

The vaccines to be administered in this study are described in Table 7.

Table 7: Investigational Product and Active Comparator Administered

Study Arm:	**mRNA-1273**	**mRNA-1273.529**	**mRNA-1273.214**
Intervention Name:	mRNA-1273 (aka, Moderna COVID-19 Vaccine)	mRNA-1273.529	mRNA-1273.214
Type:	Vaccine	Vaccine	Vaccine
Dosage Level(s):	50 µg (mRNA)	50 µg (mRNA)	50 µg (mRNA)
Route of Administration:	IM injection	IM injection	IM injection
Physical Description:	Sterile liquid for injection, white-to-off-white dispersion	Sterile liquid for injection, white-to-off-white dispersion	Sterile liquid for injection, white-to-off-white dispersion
Source:	Sourced locally by the sites	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	mRNA-1273 will be provided in its commercial presentation	mRNA-1273.529 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.	mRNA-1273.214 will be provided in 2R borosilicate glass vials. Vials will be labeled as required per local requirement.

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid.

mRNA-1273 is a LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2.

mRNA 1273.529 contains mRNA CX-031302 encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). mRNA 1273 contains mRNA CX-024414 encoding for the S-2P of Wuhan-Hu-1. mRNA-1273.214 is a bivalent vaccine containing mRNA-1273.529 and mRNA-1273 co-formulated at a 1:1 ratio. mRNA-1273.529, mRNA-1273, and mRNA-1273.214 each consists of mRNAs formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG 2000 DMG.

mRNA-1273.529, mRNA-1273, and mRNA-1273.214 will be administered at a 50 µg dose level as an IM injection into the deltoid muscle on Day 1.

6.2. Randomization and Blinding

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

As the appearance of the study vaccines differ, enrollment will be observer-blinded 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. The unblinded site personnel will prepare the dose out of view of the participant and the blinded site personnel. These personnel will have no study functions other than investigational product (IP) management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency. Once the injection is completed, only the blinded clinic staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.

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.

Except in the case of medical necessity and optional unblinding (Section 6.3.7), a participant's treatment should not be unblinded without the approval of the Sponsor. The treatment code should be broken only if the investigator in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine. Instructions regarding emergency unblinding will be provided to the investigator and are discussed in Section 6.3.7.

The investigator, clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the unblinding occurs (Section 6.3.7) or until study database is locked and unblinded for the final analysis. At the planned analyses (see Section 9.7), pre-identified Sponsor team members and selected contract research organization (CRO) team members will be unblinded to conduct the analyses.

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Clinical Study Material Preparation

The IP will be prepared for each participant based on their vaccination group assignment. The mRNA-1273.529 vaccine injection will have a volume of 0.25 mL and will contain mRNA-1273.529 at a dose of 50 µg. The mRNA-1273.214 vaccine will have a volume of 0.25 mL and will contain mRNA-1273.214 at the dose of 50 µg. The active comparator (mRNA-1273) will be administered at a volume of 0.25 mL and will contain mRNA-1273 at a dose of 50 µg. The mRNA-1273.529, mRNA-1273.214, and mRNA-1273 preparation instructions are detailed in the Pharmacy Manual.

6.3.2. Clinical Study Material Administration

The study vaccine will be administered as a single IM injection into the deltoid muscle 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 SoE (Table 1 and Table 2).

The clinic will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either onsite 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 and administration of mRNA-1273.529, mRNA-1273.214, and active comparator (mRNA-1273) are described in the Pharmacy Manual.

6.3.3. Clinical Study Material Packaging and Labeling

The Sponsor will provide the investigator (via the clinic pharmacy) with adequate quantities of the IP.

mRNA-1273.529 is provided as a sterile solution for injection at a concentration of 0.2 mg/mL in 20 mM Tris buffer with sucrose, at pH 7.5 and presented in 2R United States Pharmacopeia (USP) Type I borosilicate glass vials with PLASCAP vial seal containing a 13 mm FluroTec

coated plug stopper with a 0.8 mL nominal fill volume. mRNA-1273.529 will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

mRNA-1273.214 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 United States Pharmacopeia (USP) Type I borosilicate glass vials with PLASCAP vial seal containing a 13 mm FluroTec coated plug stopper with a 0.8 mL nominal fill volume. mRNA-1273.214 will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

mRNA-1273 injection will be sourced locally as commercial supply.

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

Updates to this clinical study material packaging and labeling information may be provided in the Pharmacy Manual or associated Commercial Packaging and will supersede the information provided in the protocol.

6.3.4. Clinical Study Material Storage

mRNA-1273 must be stored in accordance with commercial packaging in a secure area with limited access until they are prepared for administration. mRNA-1273.529 and mRNA-1273.214 must be stored at -90°C to -60°C (-130°F to -76°F) 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. It is recommended that there should be an available backup freezer. It is also recommended that 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.

Clinical study material storage requirements presented in the protocol may be superseded in accordance with requirements provided with the IP label.

6.3.5. Clinical Study Material Accountability

The investigator is responsible for ensuring the IP accountability staff maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study vaccines, 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 site monitor during site visits and at the completion of the study. For further direction, refer to the Pharmacy Manual.

6.3.6. Clinical Study Material Handling and Disposal

A site monitor will reconcile the clinical study material during study conduct 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 clinic 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.

6.3.7. Unblinding

Participants who report eligibility to receive an additional booster outside of the mRNA-1273-P305 study have the option to be unblinded in Part 1 of the study after the completion of their scheduled Month 6 visit and in Part 2 after the completion of their scheduled Month 3 visit. Unblinding may be performed remotely over the phone prior to signing the updated informed consent form (ICF) based on participant preference. Both unblinded and blinded participants will continue to follow the Schedule of Events (Section 1.3).

Except in the case of medical necessity and as part of the unblinding described above, a participant's treatment assignment 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. 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 unblindings will be tracked via an audit trail in IRT and documented in the final study report.

6.4. Study Intervention Compliance

All vaccinations will be administered by qualified and trained study personnel to ensure that all vaccine doses administered comply with those planned. Study vaccine doses administered will be recorded in the electronic case report form (eCRF). Administration data will be reconciled with site accountability records to determine compliance.

6.5. Prior and Concomitant Medications

6.5.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

6.5.2. Concomitant Medications and Therapies

At the study site, study staff must question the participant regarding any concomitant medications taken and non-study vaccinations received by the participant and record the following information in the eCRF:

- Any vaccine (authorized or investigational) administered in the prior 28 days before the study injection.
- Seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).
- All concomitant medications taken through 28 days after the study injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- All non-study vaccines at any time during the study period after the IP injection, including any authorized or investigational COVID-19 vaccine.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Systemic steroids (≥ 10 mg/day prednisone or equivalent), immunosuppressants, immune-modifying drugs, immunoglobulins, and/or blood products administered at any time during the study period after the IP injection.
- Any concomitant medications relevant to or for the treatment of a SAE, AESI, MAAE, or AE leading to withdrawal from Day 1 through EoS.
- The participant will be asked in the electronic diary (eDiary) if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after the IP injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the clinic staff during the clinic visits after vaccination or via other participant interactions (eg, telephone calls).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Global.

If a participant takes a prohibited drug therapy, the investigator and the CRO's medical monitor will make a joint decision about continuing or withholding the study vaccination of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

6.5.3. Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant from Per-protocol Analyses

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 per-protocol (PP) analysis (analysis sets are described in Section 9.5):

- 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 ≥ 10 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).
- An authorized or licensed vaccine administered during the period from 28 days before through 28 days after vaccination, except for any licensed influenza vaccine that was administered by at least 7 days and preferably 14 days before or after vaccination.
- Any COVID-19 vaccine received outside of the study after the study vaccination.
- Immunoglobulins and/or any blood products administered during the study period.

7. DELAY OR DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced.

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If a participant desires to withdraw from the study because of an AE, the investigator will attempt to obtain agreement to follow-up with the participant until the event is considered resolved or stable and will then complete the end of study eCRF.

All data collected until the date of withdrawal or last contact of the participant will be used for the analysis.

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

- AE (specify)
- SAE (specify)
- Solicited AR or reactogenicity event (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs, solicited ARs, or reactogenicity events) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study as result of an AE, SAE, solicited AR, or reactogenicity event until resolution of the event.

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

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 (see Section 11.1.6).

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

7.2. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the clinic. The following actions must be taken if a participant fails to return to the clinic for a required clinic 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 maintaining 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 (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- Should the participant continue to be unreachable or noncompliant with clinic visits or procedures, he or she will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

The study SoE for Part 1 and Part 2 of the study can be found in Table 1 and Table 2.

8.1. Screening

Before performing any study procedures, all potential participants will sign an ICF (Section 11.1.6).

At the Screening Visit (up to 28 days for the Day 1 visit), all screening requirements, including reason for screen failure if a participant is not randomized, must be completed. The Enrollment Page in the eCRF must also be completed.

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.

8.2. Confirm Inclusion and Exclusion Criteria

All inclusion and exclusion criteria described in Section 5.1 and Section 5.2 must be met before randomization (Day 1 visit).

8.3. Demographic and Baseline Data

Demographic information relating to the participant's sex, age, race, ethnicity, height, weight, and body mass index will be recorded at the Screening Visit on the appropriate eCRF page. COVID-19 vaccine history will also be recorded at the Screening Visit on the appropriate eCRF page.

8.4. Medical History

Medical history will be collected and recorded from each participant on the appropriate eCRF page. Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page.

8.5. Randomization

Vaccination group allocation will be performed at the Day 1 visit during Phase A (blinded) as described in Section 6.2. The confirmation for study vaccine administration must be recorded on the Exposure page of the eCRF.

8.6. Physical Examination and Vital Signs

A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim

physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as a MAAE (Section 8.10.4).

Vital sign measurements include the assessment of systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once prior to vaccination and once 15 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.

The information collected will be recorded in the eCRF.

8.7. Study Vaccine Administration

A single dose vaccination (mRNA-1273.529, mRNA-1273.214, or mRNA-1273) will be administered to all participants.

After completing all prerequisite procedures prior to vaccination, the study vaccine will be administered via IM injection into the deltoid muscle. Additional details regarding vaccine administration procedure are provided in Section 6.3.2.

The participants will be observed closely (via clinical assessment including measurement of vital signs) for at least 15 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions.

8.8. Immunogenicity and Efficacy Assessments

8.8.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE (Table 1 and Table 2) for the following parameters:

- Serum binding antibody (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.
- Serum nAb level against SARS-CoV-2 as measured by pseudovirus neutralization assays.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

Measurements will be performed in a laboratory or laboratories designated by the Sponsor.

According to the ICF (Section 11.1.6), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2 vaccines, additional assay development, and the immune response across SARS-CoV-2 viruses (Section 11.1.10).

8.8.2. Vaccine Efficacy and Surveillance for COVID-19 Symptoms

Vaccine efficacy will be assessed as an exploratory endpoint in Part 1 and as a secondary endpoint in Part 2 of this study. Active surveillance for COVID-19 and SARS-CoV-2 infection will be performed in both parts of the study (see Table 1 and Table 2).

8.9. Safety Assessments

Safety assessment will include monitoring and recording of the following for each participant according to the SoE (Table 1 and Table 2):

- Solicited local and systemic ARs 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.
- Unsolicited AEs observed or reported during the 28 days following vaccination. Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to withdrawal 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 vaccination.
- Physical examination findings (if performed).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.
- 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.

8.9.1. Pregnancy Screen and Testing

A point of- -care urine pregnancy test will be performed for all female participants of childbearing potential at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At 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, if 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 8.10.6.

8.9.2. Assessments for SARS-CoV-2 Infection

Study participants will have NP swab samples collected for SARS-CoV-2 testing as specified in the SoE (Table 1 and Table 2).

For the duration of the study, participants will be directed as soon as possible and within 24 hours to obtain an approved/authorized PCR test for SARS-CoV-2 locally outside of the study according to prior National Health Service (NHS) guidance if they experience symptoms of COVID-19 as previously defined by the NHS:

- High temperature (feel hot to touch on the chest or back)
- A new, continuous cough (coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours, or worse than usual cough)
- A loss or change to sense of smell or taste

If a PCR test is unavailable locally, participants will be requested to come in for a study visit or take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2.

Participants will be directed as soon as possible and within 24 hours to take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2 if they experience any of the following (but do not meet the symptoms of COVID-19 as previously defined by the NHS and described above):

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) with modifications:
    - Chills
    - Cough (not meeting COVID-19 symptoms defined by the NHS)
    - Shortness of breath or difficulty breathing
    - Fatigue
    - Muscle or body aches
    - Headache
    - Sore throat
    - Congestion or runny nose
    - Nausea or vomiting
    - Diarrhea

Lateral flow/rapid antigen test for SARS-CoV-2 may be repeated every 24-48 hours if participants continue to have symptoms above.

Participants will be directed to take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2 within 4 to 6 days after last exposure* (see definition of last exposure below) if a participant experiences the following:

- Known 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 (hugged or kissed them)
    - Sharing eating or drinking utensils
    - Being sneezed or coughed upon or getting respiratory droplets on the participant

**Last exposure is defined as the last day a participant was in close contact with a symptomatic person in the household (if the participant was then isolated from that person) or the last day of the quarantine of the person the participant was exposed to, if that person was asymptomatic and/or the participant was unable to isolate from that person.*

A study illness visit (study site visit) will be arranged as soon as possible and within 72 hours for participants who test positive or equivocal for SARS-CoV-2 using an authorized/approved lateral flow/rapid antigen or local PCR testing. If a test for SARS-CoV-2 is unavailable or if there is uncertainty on the test result, a study site visit may be arranged as soon as possible and within 72 hours.

At this visit, an NP swab will be collected to evaluate for the presence of SARS-CoV-2 infection.

Active surveillance for COVID-19 will be conducted throughout the study as described in the SoE (Table 1 and Table 2).

All cases that have RT-PCR-confirmed COVID-19 as defined by the NHS or the CDC 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) PaO2/FiO2 ratio, respiratory failure, oxygen support, shock, organ dysfunction, and life-sustaining treatment.

In addition to SARS-CoV-2 assessment and testing outlined in this protocol, also follow local testing guidelines.

8.9.3. Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site 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 SoE (Table 1 and Table 2).

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 8.10.13). 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 contact. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

8.9.4. Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their own device or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participants will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 8.10.3). Participants will also use the eDiary to respond to questionnaires related to COVID-19 (as part of active surveillance) every 2 weeks from Day 43 through Day 359/EoS.

Participants will be instructed on Day 1 on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment of localized axillary swelling or tenderness on the same side as the injection arm.

Participants will record data into the eDiary starting approximately 15 minutes after injection under supervision of the study staff to ensure successful entry of assessments. The clinic staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection, and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic ARs, as defined in Section 8.10.3, that occur on the day of vaccination and during the 7 days after vaccination (ie, the day of injection and 6 subsequent days).
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the

clinic. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.

- Measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler provided by the clinic.
- Any medications taken to treat or prevent pain or fever on the day of injection or for the next 6 days.

The eDiary should be the primary source document allowed for solicited systemic or local ARs (including body temperature measurements) up to Day 7 post vaccination. Participants will be instructed to complete eDiary entries daily. The participant will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of the solicited ARs.

Any new safety information reported during safety telephone calls or at clinic visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered in the SAR section of the eCRF.

Clinic staff will review eDiary data with participants at a visit 7 days after the injection.

8.9.5. Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant will not exceed 450 mL for each part of the study.

8.9.6. Ancillary Supplies for Participant Use

Clinics will distribute Sponsor provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions, for recording solicited ARs in the eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

8.10. Safety Definitions

8.10.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug/vaccine in humans, whether or not considered related to the drug/vaccine.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to IP or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, after the IP injection
- New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study

Events NOT Meeting the Adverse Event Definition

- Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure)
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, 7 days after vaccination).

8.10.2. Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to IP.
- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur

during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.

- **Persistent or significant incapacity or substantial disruption of the 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or 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 medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.10.3. Solicited Adverse Reactions

The term “reactogenicity” refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.9.4). Participants will record such occurrences in an eDiary on the day of IP injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entries into the eDiary according to the grading scales presented in Table 8, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR starts more than 7 days after dosing, it should be captured on the AE page until resolution, not to exceed 28 days after vaccination.

If a solicited local or systemic AR continues beyond 7 days after dosing, the participant should notify the site to provide an end date and close out the event.

ARs beyond Day 7 should be reviewed by the clinic staff either during the next scheduled telephone call or at the next clinic visit, or during an unscheduled visit.

All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 8: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[1] (Life-threatening)
Local					
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or 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	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily	Requires emergency room visit or

				activity	hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; 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

[1.] Grading of Grade 4 events will be determined per investigator and assessment is recorded on the reactogenicity event page in the electronic case report form.

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

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (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 withdrawal)
- Solicited local or systemic AR continuing beyond 7 days post injection
- Solicited local or systemic AR that leads to participant withdrawal from IP
- Solicited local or systemic AR that otherwise meets the definition of an SAE

8.10.4. Medically Attended Adverse Events

A MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a clinic for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up,

COVID-19) and visits to HCPs external to the clinic (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured on the AE page of the eCRF.

All PCR-confirmed COVID-19 cases will be recorded as MAAEs under the AE term of "COVID-19." Cases of participants who test positive using an approved/authorized lateral flow/rapid antigen test and report symptoms of COVID-19 as defined by the NHS or the CDC (Section 8.9.2) but test negative by PCR or are unable to obtain PCR testing within 2 weeks of symptom onset will be recorded as an AE.

8.10.5. Adverse Event 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.

A complete list of AESIs for this protocol are listed in Section 11.3. Additional information for anaphylaxis (Section 8.10.5.1) and myocarditis/pericarditis (Section 8.10.5.2) 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 electronic data capture system. If a site received a report of a new AESI from a participant or receives updated information on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox (see Section 8.10.11).

8.10.5.1. 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. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, per Section 8.10.11. The investigator will submit any updated anaphylaxis 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

8.10.5.2. Myocarditis/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 (see Section 8.10.2).

An independent Cardiac Event Adjudication Committee (CEAC) will be utilized and is described in Section 8.11.

The CDC Working Case Definitions are provided in Section 11.4 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.

8.10.6. Recording and Follow-up of Pregnancy

Female individuals who have a positive pregnancy test at the Screening Visit should not be enrolled; participants who have a positive pregnancy test 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 the Screening Visit and Day 1 (Table 1 and Table 2).

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

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to the Sponsor or designee within 24 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the clinic to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

8.10.7. Recording and Follow-up of an AE and/or SAE

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected from Day 1 through 7 days after the vaccine dose (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected from Day 1 through 28 days after the vaccine dose (ie, the day of injection and 27 subsequent days).

Medically attended AEs, SAEs, AESIs, and AEs leading to withdrawal will be collected from participants as specified in the SoE (Table 1 and Table 2) from Day 1 until the end of their participation in the study. Any AEs occurring before receipt of IP will be analyzed separately from TEAEs.

At every clinic visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including surveillance for respiratory viral infection symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, physical examination findings and other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and

followed until resolution, stabilization, the event is otherwise explained, the participant is LTFU (Section 7.2), or the participant withdraws consent (Section 7.1).

8.10.8. 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 8.10.2), 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. Specific criteria for local and systemic reactogenicity events are presented in Section 8.10.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Clinic staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.10.9. Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

8.10.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes, type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

8.10.11. Reporting Serious Adverse Events

Any AE considered serious by the investigator or that meets SAE criteria (Section 8.10.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE. The investigator is responsible for notifying the independent ethics committee (IEC) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline: 08-009175406
- SAE Fax line: 08-082340330

Regulatory reporting requirements for SAEs are described in Section 8.10.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the participant to discontinue the study.

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

Medical occurrences that begin before the start of IP administration but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

AEs may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant
- Questioning the participant in an unbiased and nonleading manner

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of becoming aware of the event, as indicated in Section 8.10.2. 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 AEs or SAEs after conclusion of the study participation (EoS). However, if an investigator learns of any SAE, including a death, at any time after a participant has completed or withdrawn from the study and considers the event to be reasonably related to the study IP or study participation, the investigator must promptly notify the Sponsor.

8.10.13. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. At the time of consent, the participants 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. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of vaccination 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.

8.10.14. 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 AEs, SAEs, and AESIs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, the participant is LTFU (Section 7.2), or the participant withdraws consent (Section 7.1).

8.10.15. 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 towards 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, IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

For the mRNA-1273-P305 study, events of anaphylaxis, myocarditis and pericarditis that are assessed as serious and related by the Investigator will be reported in an expedited manner to the local regulatory authority by the Sponsor, and mRNA-1273-P305 study IECs and Investigators will be notified, if appropriate according to local requirements.

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 IEC, if appropriate according to local requirements.

8.11. Safety Oversight

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and CRO medical monitor, as well as safety reviews by an unblinded Data and Safety Monitoring Board (DSMB). The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB, composed of external, independent subject matter experts, including an unblinded statistician, will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for “probable” or “confirmed” events (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.

8.12. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 11.1.8).

8.13. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.14. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.15. Biomarkers

Biomarker assessments (to be determined) will be evaluated as part of the study.

9. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study focusing on the randomized, blinded phase (Phase A) of the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study. If changes are made to primary and/or secondary objectives or the related statistical methods after the study has begun, 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 clinical study report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR. Statistical analyses of the open-label, observational phase (Phase B) will be provided in the SAP.

9.1. Blinding and Responsibility for Analyses

Phase A of this study is observer-blind. 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 6.3.7) or until study database is locked and unblinded, with the following exceptions:

- An independent unblinded statistical and programming team who are not involved in study design and conduct of the CRO will perform the planned primary analysis, (Section 9.7). Select Sponsor team members including biostatistician and statistical programmers will be prespecified to be unblinded to the primary analysis results and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants. The details will be included in the Data Blinding Plan.
- The DSMB may review data, as appropriate, to safeguard the interests of clinical study participants and to help ensure the integrity of the study.

Procedures for breaking the blind in the case of a medical necessity are provided in Section 6.3.7.

9.2. Statistical Hypotheses

Part 1:

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

Primary Hypotheses:

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

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

Key Secondary Hypothesis:

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

For the primary objective of immune response, hypotheses testing based on participants receiving the 4th dose, alpha of 0.05 (2-sided) will be allocated to the 2 time points: alpha of 0.01 (2-sided) will be allocated to Day 29, alpha of 0.04 (2-sided) will be allocated to Month 3.

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Day 29 will be assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.01. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain is demonstrated, ie, the lower bound of the 99% confidence interval (CI) of the GMT ratio of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is $\geq$ 0.67 (1/1.5).

The non-inferiority of mRNA-1273.529 as compared to mRNA-1273 against the B.1.1.529 strain at Month 3 will be assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.04. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain is demonstrated, ie, the lower bound of the 96% confidence interval (CI) of the GMT ratio of mRNA-1273.529 vs. mRNA-1273 against B.1.1.529 is $\geq$ 0.67 (1/1.5).

Part 2:

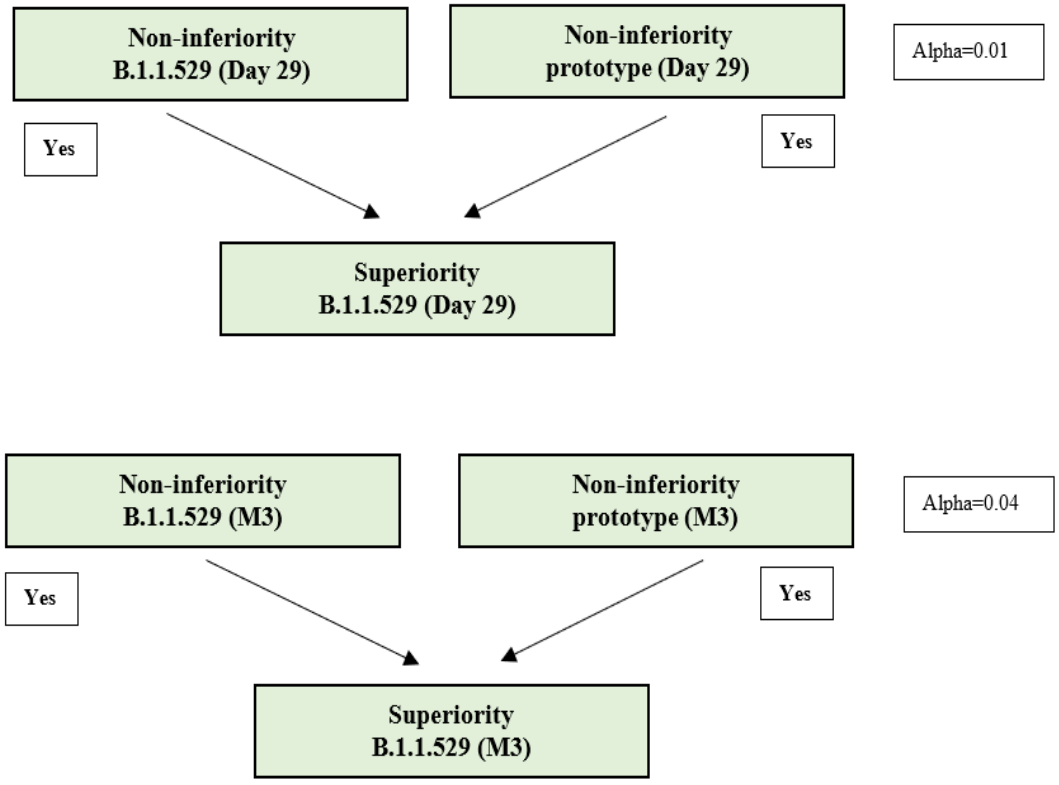
The primary objective on immune response in Part 2 of this study is based on the participants who will receive the 4th dose in Part 2 of the study. There are 6 hypotheses on immune response of mRNA-1273.214 listed below. Part 2 of this study is considered to have met its primary objective if non-inferiority of mRNA-1273.214 against the B.1.1.529 strain, non-inferiority of mRNA-1273.214 against the prototype strain, and superiority of mRNA-1273.214 against the B.1.1.529 strain are demonstrated as compared to mRNA-1273 at Day 29 or Month 3. Figure 2 depicts the hypotheses testing strategy.

Primary Hypotheses:

1) mRNA-1273.214, as a single booster dose, is non-inferior to mRNA-1273 based on GMT ratio against the B.1.1.529 strain with a non-inferiority margin of 1.5 at Day 29.
2) mRNA-1273.214, as a single booster dose, is non-inferior to mRNA-1273 based on GMT ratio against the prototype strain with a non-inferiority margin of 1.5 at Day 29.

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

Figure 2: Statistical Hypothesis Testing Strategy of mRNA-1273 vs. mRNA-1273 (Part 2)



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

For the primary objective of immune response, hypothesis testing based on participants receiving the 4th dose, alpha of 0.05 (2-sided) will be allocated to the 2 timepoints: alpha of 0.01 (2-sided) will be allocated to Day 29, and alpha of 0.04 (2-sided) will be allocated to Month 3.

For the primary immunogenicity objective, the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain and the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the prototype strain at Day 29 will be assessed using a non-

inferiority margin of 1.5 at 2-sided alpha of 0.01. The primary immunogenicity objective is considered met if non-inferiority against the B.1.1.529 strain and the prototype strain are both demonstrated, ie, the lower bound of the 99% confidence interval (CI) of the GMT ratio of mRNA-1273.214 vs. mRNA-1273 against B.1.1.529 is ≥ 0.67 (1/1.5) and the lower bound of the 99% CI of the GMR of mRNA-1273.214 vs mRNA-1273 against prototype is ≥ 0.67.

Superiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain will be evaluated at Day 29. Once the non-inferiority of mRNA-1273.214 as compared to mRNA-1273 against the B.1.1.529 strain and against the prototype strain is demonstrated, the 99% CI of GMT ratio (mRNA-1273.214 vs. mRNA-1273) will be used to assess superiority of mRNA-1273.214 as compared to mRNA-1273. If the lower bound of the GMT ratio rules out (>) 1 at Day 29, superiority of mRNA-1273.214 compared to mRNA-1273 against B.1.1.529 will be considered demonstrated.

Hypotheses testing at Month 3 will be performed in the same manner, first testing 2 non-inferiority hypotheses (one against the B.1.1.529 strain and one against the prototype strain) at alpha of 0.04 level (2-sided). Once non-inferiority is demonstrated for both B.1.1529 and prototype strains, then superiority testing against the B.1.1.529 at alpha of 0.04 level (2-sided) will be performed.

9.3. Sample Size and Power Calculation

This study will include:

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

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

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

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

The target enrollment is approximately 500 participants for each study arm (1:1). The assumptions are: 1) at least CCI participants will be in 4th dose subgroup; and 2) CCI of

participants will be excluded from the PP set for immunogenicity, SARS-CoV-2 negative (eg, due to infection with the SARS-CoV-2 Omicron variant).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, 2-sided):

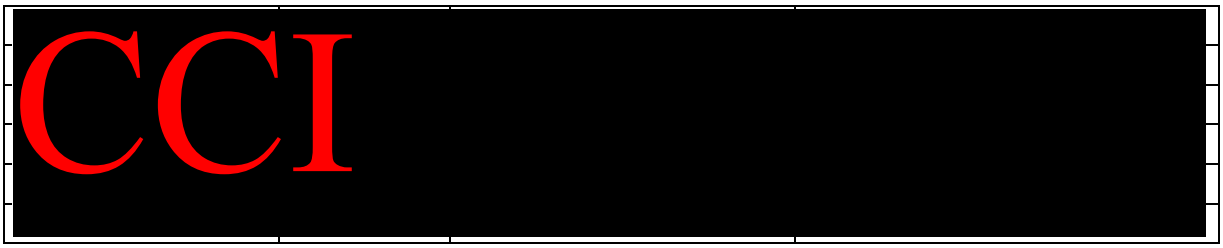
With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at 2-sided alpha of 1.0% at Day 29. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a 2-sided alpha of 1% at Day 29 ranges from CCI The assumptions are: the true GMT ratio (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

Statistical power for hypotheses testing at Month 3 (alpha=0.04, 2-sided):

With approximately CCI evaluable participants per arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.529 against the B.1.1.529 strain at 2-sided alpha of 4.0% at Month 3. With this range of sample sizes, the power to demonstrate superiority of mRNA-1273.529 against the B.1.1.529 variant strain at a 2-sided alpha of 4% at Month 3 ranges from CCI. The assumptions are: the true GMT ratio (mRNA-1273.529 vs mRNA-1273) ranges from CCI, the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5. Specific operating characteristics for Part 1 are provided in Table 9. With approximately CCI participants receiving the 4th dose in each study arm, there is at least 90% probability to observe one participant reporting an AE in each study arm if the true incidence of AEs is 1%.

Table 9: Operating Characteristics and Power for the Primary and Key Secondary Objectives Under Various GMR and the Number of Evaluable Participants with Immunogenicity Data Who Receives the 4th Dose in this Study (Part 1)

True GMR (mRNA-1273.529 vs. mRNA-1273 against B.1.1.529)	Number evaluable patients per arm (4th dose)	Minimum empirical GMR for the primary objective	Power
Two-sided Type I Error (α) = 0.01 (Day 29)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
Key Secondary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			
1.1			3%
Two-sided Type I Error (α) = 0.04 (Month 3)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
1.1			90%
Key Secondary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			



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

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

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

Hypotheses testing on immunogenicity data will be performed at 2 timepoints of interest (Day 29 and Month 3 post booster). To preserve family-wise alpha of 0.05 (2-sided), alpha will be allocated to Day 29 of 0.01 (2-sided), and Month 3 of 0.04 (2-sided).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, 2-sided):

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

Statistical power for hypotheses testing at Month 3 (alpha=0.04, 2-sided):

With approximately CCI evaluable participants in each arm, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 against the B.1.1.529 strain and against prototype at 2-sided alpha of 4.0% at Month 3. With this sample size, there is approximately CCI power to demonstrate superiority of mRNA-1273.214 against the B.1.1.529 variant strain at a 2-sided alpha of 4.0% at Month 3. The assumptions are: the true GMT ratio (mRNA-1273.214 vs. mRNA-1273) against the B.1.1.529 strain ranges from CCI and the true GMT ratio (mRNA-1273.214 vs. mRNA-1273) against the prototype strain is [redacted], the standard deviation of the natural log-transformed titer is CCI, with a non-inferiority margin of 1.5.

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

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

Table 10 includes the power and operating characteristics under various GMT ratios and 2 different scenarios for the number of evaluable participants with immunogenicity data. Based on CCI evaluable participants per arm (4th dose), under the same assumptions outlined above, there is CCI power to demonstrate non-inferiority of mRNA-1273.214 compared to mRNA-1273 against B.1.1.529 at Day 29 at $\alpha = 1\%$ if true GMT ratio CCI; and there is approximately CCI power to demonstrate superiority at $\alpha = 1\%$ if the true ratio if CCI. With this size, there is CCI power at Month 3 (primary objective) at $\alpha = 4\%$ (2-sided) if the true GMR is CCI; and CCI power to demonstrate superiority at $\alpha = 4\%$ (2-sided) if the true GMR is CCI.

Table 10: Operating Characteristics and Power for the Primary and Key Secondary Objectives Under Various GMR and the Number of Evaluable Participants with Immunogenicity Data Who Receives the 4th Dose in this Study (Part 2)

True GMR (mRNA-1273.214 vs. mRNA-1273 against B.1.1.529)	Number evaluable patients per arm (4th dose)	Minimum empirical GMR for the primary objective	Power
Two-sided Type I Error (α) = 0.01 (Day 29)			
Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)			
CCI			
Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)			
CCI			
Two-sided Type I Error (α) = 0.04 (Month 3)			

Primary Objective: Non-inferiority (lower bound of the (1-α) *100% of GMR ≥ 0.67)
CCI
Primary Objective: Superiority (lower bound of the (1-α) *100% of GMR rules out 1)
CCI

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

9.4. Multiplicity

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

9.5. Analyses Populations

The analysis populations for Part 1 and Part 2 are defined in Table 11.

Table 11: Populations for Analyses

Set	Description
Full Analysis Set (FAS)	The FAS consists of all randomized participants who receive the IP. Participants will be analyzed according to their randomized study arm.
Modified Intent-to-Treat (mITT) Set	The mITT Set consists of all participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) prebooster, ie, all FAS participants with pre-booster/baseline SARS-CoV-2 negative status. Participants will be analyzed according to their randomized study arm.
PP Set for Immunogenicity (PPSI)	The PPSI consists of all participants in the FAS who receive 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.
PP Set for Immunogenicity – SARS-CoV-2 negative (PPSI-Neg)	Participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection up to day of visit analysis, ie, who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid. PPSI-Neg will be the primary analysis set for analyses of immunogenicity unless otherwise specified.
Solicited Safety Set	The Solicited Safety Set consists of all randomized participants who receive IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the study arm that they actually received.
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.
PP Set for Efficacy (PPSE)	The PPSE consists of all participants in the mITT who receive the planned study vaccination and have no major protocol deviations that impact key or critical data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PP = Per-protocol; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

9.6. Statistical Analyses

This section provides a summary of the planned statistical analyses of the primary and secondary objectives in Phase A (randomized, blinded). The SAP will be developed and finalized before the first planned analysis (Section 9.7).

9.6.1. Immunogenicity Analyses

Part 1: An analysis of covariance (ANCOVA) model will be performed to assess the difference in immune response between mRNA-1273.529 and mRNA-1273 as the 4th dose in the subgroup of participants who received the 4th dose. This analysis will be carried out for immune response against the B.1.1.529 strain and the prototype virus strain separately in the PPSI-Neg analysis population.

Specifically, for immune response against the B.1.1.529 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.529 and mRNA-1273) will be the fixed effect, adjusting for age groups ($< 65, \geq 65$ years) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the geometric least square mean (GLSM) from the model and its corresponding 99% CIs will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.529 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 99% CIs will be provided. The 99% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for mRNA-1273.529 at Day 29 compared to the mRNA-1273 as a booster for non-inferiority testing.

Against the B.1.1.529 strain, the non-inferiority of immune response of mRNA-1273.529 as compared to mRNA-1273 will be considered demonstrated if the lower bound of the corresponding 99% CI is ≥ 0.67 (Day 29) based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 is demonstrated, superiority of mRNA-1273.529 as compared to mRNA-1273 against B.1.1529 will be tested; if the lower bound of the 99% CI of the GMT ratio is > 1 (Day 29), superiority is demonstrated.

The same ANCOVA model will be used to assess immune response of mRNA-1273.529 against the B.1.1.529 strain at Month 3; the 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority and superiority. For the immune response against the prototype virus strain, the same analysis method will be used.

Part 2:

An ANCOVA model will be carried out to assess the difference in immune response between mRNA-1273.214 and mRNA-1273 in the subgroup of participants who received the 4th dose. This analysis will be carried out for immune response against the B.1.1.529 strain and the prototype virus strain separately using the PPSI-Neg analysis population.

Specifically, for immune response against the B.1.1.529 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the B.1.1.529 strain will be a dependent variable, and a group variable (mRNA-1273.214 and mRNA-1273) will be the fixed effect, adjusting for age groups (< 65, ≥ 65 years) and pre-booster antibody titer level, if applicable. The GMT will be estimated by the geometric least square mean (GLSM) from the model and its corresponding 99% CIs will be provided for each group. The GMR (ratio of GMTs) for mRNA-1273.214 with respect to mRNA-1273 will be estimated by the ratio of GLSM from the model and the corresponding 99% CIs will be provided. The 99% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for mRNA-1273.214 at Day 29 compared to the mRNA-1273 as a booster for non-inferiority testing.

Against the B.1.1.529 strain, the non-inferiority of immune response of mRNA-1273.214 as compared to mRNA-1273 will be considered demonstrated if the lower bound of the corresponding 99% CI is ≥ 0.67 based on a non-inferiority margin of 1.5.

Once non-inferiority against B.1.1.529 is demonstrated, superiority of mRNA-1273.214 as compared to mRNA-1273 against B.1.1529 will be tested (at Day 29); if the lower bound of the 99% CI of the GMT ratio is > 1, superiority is demonstrated.

The same ANCOVA model will be used to assess immune response of mRNA-1273.214 against the B.1.1.529 strain at Month 3. The 96% CI for GMR will be used to assess the between group difference in immune response against the B.1.1.529 strain for non-inferiority and superiority. For the immune response against the prototype virus strain, the same analysis method will be used.

As part of the secondary analysis to assess for immune response against other variants, the same analysis method described above will be used. A 95% CI for GMR will be used to assess for non-inferiority and superiority.

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

Immunogenicity, SARS-CoV-2-specific bAb and nAb, will be assessed at multiple time points in this study. Mixed effects models will be used to analyze all post-booster/baseline measures. The models will include treatment group, analysis visit, treatment by visit interaction, and adjustment for age groups and pre-booster titer levels. 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 (ratio of GMTs) for mRNA-1273.529 and for mRNA-1273.214 with respect to mRNA-1273 will be estimated from each model and the corresponding 95% CI will be provided at each post-boost time point.

For each of the antibodies of interest (eg, levels of SARS-CoV-2–specific bAb and SARS-CoV-2-specific nAb), the GMT or level with corresponding 95% CI at each time point, and GMFR of post-booster/pre-booster titers or levels with corresponding 95% CI at each post baseline time point will be provided for each arm. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: number of participants (n), median, minimum, and maximum. PPSI will be used as the analysis population to summarize the immune responses (antibodies of interest) and will the above summary statistics including GMT and GMFR will be provided by pre-booster/study baseline SARS-CoV-2 status.

SRR definitions and analyses will be defined in the SAP.

9.6.2. Efficacy Analyses

Number and incidence rates of symptomatic COVID-19 disease, asymptomatic SARS-CoV-2 infection, as well as COVID-19 regardless of symptoms will be provided for each study arm. Vaccine efficacy may be estimated if the number of cases accrued is deemed to be sufficient. Efficacy analyses will be performed using the mITT and PP Set for Efficacy analysis populations and the details will be provided in SAP.

9.6.3. Safety Analyses

All safety analyses will be based on the Safety Set, except analyses of solicited ARs, which will be based on the Solicited Safety Set.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic ARs), unsolicited AEs, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after vaccination, and with Grade 3 or higher solicited AR will be provided. A 2-sided 95% exact CI using the Clopper Pearson method will be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be summarized. The follow-up windows for AEs are detailed in the SoE (Table 1 and Table 2). Unsolicited AEs will be presented

by MedDRA system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

Pregnancy outcomes will also be summarized.

Table 12 summarizes the analysis strategy for safety parameters. Further details will be described in the SAP.

Table 12: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	X	X
Any unsolicited AE	X	—
Any SAE	X	—
Any AESI	X	—
Any unsolicited MAAE	X	—
Any unsolicited treatment-related AE	X	—
Any treatment-related SAE	X	—
Discontinuation due to AE	X	—
Any severe AE	X	—
Any treatment-related severe AE	X	—

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by SOC and PT coded by MedDRA.

9.6.4. Exploratory Analyses

For the exploratory analyses for mRNA-1273.529 or mRNA-1273.214 against other variants (eg, Alpha, Beta, Delta), the same analyses methods described in Section 9.6.1 will be employed to analyze immunogenicity data.

9.7. Planned Analyses

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

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. APPENDIX 1: Study Governance Considerations

11.1.1. 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 Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.
- Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
  - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.1.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives may visit the investigational clinic to:

- Determine the adequacy of the facilities.

- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor, designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IEC review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.1.3. Audits and Inspections

The Sponsor, their designee(s), the IEC, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IEC, or regulatory authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The Principal Investigator must obtain IEC approval for the investigation. Initial IEC approval and all materials approved by the IEC for this study, including the participant consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

11.1.4. Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the clinic are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the clinic are not financially responsible for further treatment of the disease under study.

11.1.5. Recruitment Procedures

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 IEC.

11.1.6. Informed Consent Process

The informed consent document(s) must meet the requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IEC or study center. All consent documents will be approved by the appropriate IEC.

The actual ICF used at each center may differ, depending on local regulations and IEC requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC prior to the form being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him or her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his or her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate.

The participant must be made aware of and give consent to direct access to his or her source medical records by study monitors, auditors, the IEC, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant should also be informed that he or she is authorizing such access by signing the ICF.

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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial screening period).

The ICF will contain a separate consent form(s) that addresses the use of remaining optional samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. A participant will be told that they are free to refuse participation and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document agreement to allow any remaining specimens to be used for exploratory research. A participant who declines to participate in this optional research will not provide this separate signature.

11.1.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IEC(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed to by the investigator(s), and approved by the relevant IEC(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IEC(s) must be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigator(s), and notified to the IEC(s).

11.1.8. Protocol Deviations

The noncompliance may be either on the part of the participant, the investigator, or the clinic staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within a timely manner of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Sponsor and the study medical monitor. Protocol deviations must be sent to the reviewing IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IEC requirements.

11.1.9. 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 his or her 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.

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

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his or her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

11.1.10. Sample Retention and Future Biomedical Research

The retention period of laboratory samples will be 20 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1273/mRNA-1273.529/mRNA-1273.214 or anti-respiratory virus immune response. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity to SARS-CoV-2 to include humoral and cellular immune assay methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273/mRNA-1273.529/mRNA-1273.214 as well as to determine how changes in biomarkers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from

new scientific findings related to the drug class or disease, as well as reagent and assay availability.

11.1.11. Data and Safety Monitoring Board

A DSMB will be used throughout the conduct of this study. The DSMB will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. The data to be reviewed will be unblinded. Safety data will be reviewed according to intervals defined in the DSMB charter and as needed if potential safety concerns are identified.

11.1.12. 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 clinical trial register (eu.ctr), etc., as well as some national registries.

11.1.13. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in an eCRF 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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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 Clinical 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).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion 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.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed, and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

11.1.14. Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the investigational site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using the WHO-drug reference list.

11.1.15. 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 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 case report form 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 Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts and the signed ICFs forms are to be included in the investigator's files with the participant's study records.

11.1.16. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.17. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IEC(s), the regulatory authorities, and any CRO(s) 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.

The Sponsor or designee reserves the right to close the clinic or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate clinic 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 clinic by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further mRNA-1273 development.

Clinics will be closed upon study completion. A clinic is considered closed when all required documents and study supplies have been collected and a clinic closure visit has been performed.

11.1.18. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, 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.

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov. The results of and data from this study belong to the Sponsor.

11.2. APPENDIX 2: Contraceptive Guidance

Definitions: Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche

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 follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 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
- Documented tubal ligation
- 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.

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)
- 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.

11.3. APPENDIX 3: Adverse Events of Special Interest

Investigators should report all events which fall into the categories presented in Table 13 as an AESI per the reporting processes specified in Section 8.10.5. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Table 13: Adverse Events of Special Interest

Medical Concept	Additional Notes
Anosmia, Ageusia	New onset coronavirus disease (COVID)-associated or idiopathic events without other etiology excluding congenital etiologies or trauma.
Subacute thyroiditis	Including but not limited to events of atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis, and thyroiditis.
Acute pancreatitis	• Including but not limited to events of autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis. • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures).
Appendicitis	Include any event of appendicitis.
Rhabdomyolysis	New onset rhabdomyolysis without known etiology such as excessive exercise or trauma.
Acute respiratory distress syndrome	Including but not limited to new events of acute respiratory distress syndrome and respiratory failure.
Coagulation disorders	Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, and deep vein thrombosis.
Acute cardiovascular injury	Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction.

Acute kidney injury	• Include events with idiopathic or autoimmune etiologies
	• Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast agents, etc)
	• Include all cases that meet the following criteria:
	  ○ Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 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; OR
	  ○ Urine volume ≤ 0.5 mL/kg/hour for 6 hours.

Medical Concept	Additional Notes
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria: o > 3-fold elevation above the upper normal limit for alanine transaminase or aspartate aminotransferase OR o > 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 adverse reactions including but not limited to: Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, and fixed drug eruptions.
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults • Multisystem inflammatory syndrome in children • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 $\times 10^9$ per mm^3 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome.
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma).
New onset of or worsening of neurologic disease	• Including but not limited to o Guillain-Barre syndrome o Acute disseminated encephalomyelitis o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per Section 8.10.5. • Follow reporting procedures per Section 8.10.2

Medical Concept	Additional Notes
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (includes myalgic encephalomyelitis and postviral fatigue syndrome) • Myasthenia gravis

11.4. APPENDIX 4: 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 14 as guidance.

Table 14: 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 **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 electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§ • Abnormal cardiac function or wall motion abnormalities on echocardiogram • Cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis **AND** • No other identifiable cause of the symptoms and findings	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 **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** • 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 patients 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 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.

11.5. APPENDIX 5: Protocol Amendment History

11.5.1. Amendment 1, 03 Mar 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment:

The main rationale for this amendment is to modify the study design to include 2 parts: Part 1) mRNA 1273.529 with a reduced sample size, and Part 2) mRNA 1273.214 with a similar study design to Part 1.

The summary of changes table provided below describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol. Minor grammar and formatting corrections were made throughout the document to enhance clarity and readability (which did not affect the conduct of the study).

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Cover Page, Protocol Approval Page, and 1.1 Protocol Synopsis	Removed mRNA-1273.529 (B.1.1.529) from the title	Modified to make it inclusive of mRNA-1273.214.
Global	Changed “within 3 months” to “within 90 days”	To enhance clarity
1.1 Protocol Synopsis and Section 5.2, Exclusion Criteria	Removed from Exclusion Criteria #12: “Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the Investigator.”	Removed due to redundancy

Section # and Name	Description of Change	Brief Rationale
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints	Added an objective and endpoint table for the new Part 2 (mRNA-1273.214 and mRNA-1273).	To reflect the updated study design which will now have 2 parts.
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Primary Endpoint (Part 1)	For the primary non-inferiority of the immune response of mRNA-1273.529 compared to mRNA-1273 booster administered as a 4th dose against the B.1.1.529 strain endpoint in Part 1, Month 3 was added as an assessment timepoint.	Due to revisit of the primary objectives and endpoints.
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Other Secondary Endpoints (Part 1)	For the other secondary endpoints of the evaluation of the immunogenicity of mRNA-1273.529 booster compared to mRNA-1273 booster administered at the 3rd or 4th dose in Part 1, immunogenicity will be evaluated at all measured timepoints.	Due to revisit of the Other Secondary objectives and endpoints.
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Other Secondary Endpoints (Part 1)	Changed the endpoint of evaluating the immunogenicity of mRNA-1273.529 and mRNA-1273 booster at all evaluable endpoints against the B.1.1.529 strain (and prototype strain) rather than against other strains.	To enhance clarity as the evaluation of the immunogenicity of mRNA-1273.529 booster against other variant strains is already included as an exploratory objective.
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Other Secondary	Removed the other secondary endpoint to evaluate the immunogenicity of mRNA-1273.529 and mRNA-1273 booster at all evaluable time points after the vaccination administration.	This other secondary endpoint was repetitive to the to the other secondary endpoints.
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Exploratory Endpoints (Part 1)	Removed the exploratory endpoint/objective to evaluate cellular immunogenicity of a subset of participants in Part 1.	Due to a revisit of the exploratory endpoint/objective.

Section # and Name	Description of Change	Brief Rationale
1.1 Protocol Synopsis and Section 3, Objectives and Endpoints: Part 2	Added Objectives and Endpoints for Part 2 of the study.	New objects and endpoints added to address Part 2 of the study.
1.1 Protocol Synopsis, Overall Study Design; Section 4.1, General Design	Provided study design details for Part 1 and Part 2.	To add study conduct details with the addition of mRNA-1273.214.
1.1 Protocol Synopsis, Number of Participants	Updated the section to include the approximate number of participants in Part 1 and Part 2.	Changes due to the addition of Part 2 administration of the mRNA-1273.214.
1.1 Protocol Synopsis and Section 5.1, Inclusion Criteria	Update the definition of "women of nonchildbearing potential"	To align with the updated protocol template language.
1.1 Protocol Synopsis and Section 5.2, Exclusion Criteria #1	Modified the definition of the exposure criteria for SARS-CoV-2 infection or COVID-19	Exclusion criteria updated to provide clarity.
1.1 Protocol Synopsis and Section 5.2, Exclusion Criteria #3	Modified timing of a positive PCR test from 08 November 2021 to within 90 days of Screening	To enhance clarity and accommodate the addition of mRNA-1273.214.
1.1 Protocol Synopsis, Study Treatments and Section 6.1, Investigational Product	Add Investigational product information for the mRNA-1273.214 product.	To provide additional details on the formulation of the mRNA-1273.214.
Section 8.8.2, Vaccine Efficacy and Surveillance for COVID-19 Symptoms	In Section 8.8.2, added "vaccine efficacy" to the heading.	Updated to provide details of the new study design.
1.1 Protocol Synopsis, Efficacy Assessments and Section 8.8.2, Vaccine Efficacy and Surveillance of COVID-19 Symptoms	Added surveillance for COVID-19 and SARS-CoV-2 infection to Part 2.	Added for Part 2 of the study. No changes for Part 1 of the study.
1.1 Protocol Synopsis and Section 9.2, Statistic Hypotheses	Modified the statistical hypotheses for Part 1.	Modified Part 1 and added Part 2

Section # and Name	Description of Change	Brief Rationale
	Added statistical hypotheses for Part 2.	information due to study design changes.
1.1 Protocol Synopsis, Figure 1	Added Part 2 of the study to the title of Figure 1 to summarize statistical hypotheses testing strategy for mRNA-1273.214 and mRNA-1273.	Added due to changes in study design.
1.1 Protocol Synopsis, Sample Size and Section 9.3 Sample Size and Power Calculation	Modified (Part 1) and added (Part 2) details for targeted enrollment and other sample size assumptions.	Changed Part 1 due to study design modifications and added information for Part 2.
1.1 Protocol Synopsis and Section 9.5, Analysis Populations	Clarified the analysis population definitions for the Full Analysis Set, Modified Intent-to-treat, and PP Set for Immunogenicity	Minor wording clarification
Section 9.4, Multiplicity	Added this section to describe the statistical testing in Part 1 and Part 2. Other subsequent section headings within the protocol were renumbered due to this additional heading in Section 9.4: 9.5 Analyses Populations 9.6 Statistical Analyses 9.7 Planned Analyses	Added due to the study design change.
1.1 Protocol Synopsis and Section 9.6.1, Immunogenicity Analysis (Part 1)	Modified Part 1 immunogenicity analysis.	Modified Part 1 immunogenicity analysis due to study design change.
1.1 Protocol Synopsis and Section 9.6.1, Immunogenicity Analysis (Part 2)	Added details of the immunogenicity analysis in Part 2.	Added due to the study design change.
1.1 Protocol Synopsis and Section 9.7, Planned Analysis	Removed the subheadings “primary” and “final” analysis. Changed “primary analyses” to “planned analyses” of the immunogenicity and safety. Added	Modified to provide clarity.

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	Months 3 and 6 to the planned analyses	
Section 1.2, Figure 2 Study Schema	Modified Part 1 and added new Part 2 study information.	Modified Part 1 and added Part 2 due to new study design.
Section 1.3, SoE	Deleted Screening from the SoE for Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE. Added Table 2 for new Part 2 of the study	To correct a minor error.
Section 2.2, Background; Section 2.2.1, mRNA-1273 and mRNA-1273.529; Section 2.3, Benefit/Risk Assessment; Section 4.2, Scientific Rationale for Study Design; Section 8.7, Study Vaccine Administration	Added the mRNA-1273.214 vaccine, where applicable.	To provide more details of the mRNA-1273.214 product and formulation.
Section 2.2, Background	Added sentence to state FDA approval date of Spikevax.	Updated clinical program.
Section 2.2.3, Clinical Studies	Added information regarding the preliminary data from the Phase 2 trial.	To provide information to support the testing of the bivalent mRNA-1273.214 vaccine in Part 2.
Section 10, References	Added FDA New Release to the reference section to support FDA approval.	Added due to new information on the marketing approval of mRNA-1273.
Section 6.3, Preparation/Handling/Storage /Accountability	Updated clinical study material information, administration, packaging, labeling, and storage for the mRNA-1273.214 product.	Added due to study design changes.
Section 6.3.7, Unblinding	Removed statement regarding the instructions to the investigator	Modified per regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
	communicating the unblinding of a participant.	
Section 8.9.1, Pregnancy Screen and Testing	Changed the participant's FSH level from "may" to "should" be measured at the Screening Visit, if necessary.	Modified to clarify.
Section 8.10.15, Regulatory Reporting Requirements for SAEs	Added information regarding the events of anaphylaxis, myocarditis, and pericarditis that are assessed as serious and related by the investigator to be reported in an expedited manner.	Provided details specifying that events deemed as serious and related by the investigator will be reported appropriately according to local requirements.
11.2 Appendix 2: Contraception Guidance	Updated the definition of "women of childbearing potential" and the definition of "nonchildbearing potential".	To align with the updated protocol template language.
11.2 Appendix 2: Contraception Guidance	Deleted "used in conjunction with spermicide".	To clarify what constitutes adequate contraception for practical conduct of the study.

Signature Page for VV-CLIN-004704 v3.0

2nd Approval	PPD	

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