CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls
Protocol Number:	mRNA-1273-P304
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
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Regulatory Agency Identifier Number(s):	IND: 019745
Amendment Number:	4
Date of Amendment 4:	20 Dec 2021
Date of Amendment 3:	23 Aug 2021
Date of Amendment 2:	28 Jul 2021
Date of Amendment 1:	18 June 2021
Date of Original Protocol:	31 Mar 2021

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by ModernaTX, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed written consent of ModernaTX, Inc. The study will be conducted according to the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance.*

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls

Protocol Number: mRNA-1273-P304

Amendment Number: 4

Date of Amendment: 20 Dec 2021

Protocol accepted and approved by:

See eSignature and Date in the last page

Of the document

CCI [redacted] Date

ModernaTX, Inc
200 Technology Square
Cambridge, MA 02139
Telephone: CCI [redacted]

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls" 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 Institutional Review Board (IRB) approval except to eliminate an immediate risk to participants.

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

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB. 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, US federal regulations, and ICH E6(R2) GCP guidelines.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	20 Dec 2021
Amendment 3	23 Aug 2021
Amendment 2	28 Jul 2021
Amendment 1	18 Jun 2021
Original Protocol	31 Mar 2021

Amendment 4, 20 Dec 2021: 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

The main rationale for this amendment is to offer currently enrolled participants and eligible participants who received the primary coronavirus disease 2019 (COVID-19) vaccination series (ie, Pfizer, Moderna, Janssen) outside the study to receive a booster dose. This change is being made in accordance with the recent US CDC guidance recommending a COVID-19 booster dose in people aged ≥ 18 years who are moderately and severely immunocompromised which includes solid organ transplant (SOT) recipients.

In addition, this amendment will modify the time interval requirement between informed consent and date of transplant from 6 months to 90 days to provide an opportunity for sites to enroll transplant recipients who are clinically eligible to receive the COVID-19 vaccine outside of the study.

The Summary of Changes table provided below describes the major changes made in Amendment 4 relative to Protocol Amendment 3, including the sections modified and the corresponding rationales. The synopsis of Amendment 4 has been modified to correspond to changes in the body of the protocol.

Summary of Changes in Protocol Amendment 4:

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis	Changed North America to US and non-US sites	To allow for flexibility in the location of the sites in the protocol
Throughout the protocol	Assigned each study arm with a group number	To increase clarity in the protocol

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Study Rationale, Section 1.2.2. Clinical Studies, Section 3.2. Scientific Rational for Study Design, Section 3.3 Justification for Dose and Choice of Study Population	Added in data from the mRNA-1273-P201 study.	To provide support of the booster dose.
Section 1.2.2. Clinical Studies	• Added information about the BLA submission completion. • Added Study mRNA-1273-P205.	• To update the protocol on the status of the submission. • To provide support of the booster dose.
Section 1.3.2. Risks to Study Participants and Risk Mitigation	Clarified the timeframe of myocarditis and pericarditis events (from "shortly" to "within 7 days").	To provide more specific information in the protocol.
Section 2. Objectives and Endpoints	Added objectives for the addition of Part B.	To add a new study part (Part B) to continue to evaluate the benefit-risk profile of a booster dose of mRNA-1273.
Section 1.3.3. Overall Benefit/Risk Conclusion, Section 3.1. General Design, Section 3.1.1. Study Periods, Section 3.1.1.2. Treatment Period and Follow-up Period, Section 3.2. Scientific Rationale for Study Design, Section 3.3. Justification for Dose and Choice of Study Population, Section 4.2. Study Eligibility Criteria (Part B), Section 5.2. Randomization and Stratification, Section 5.3.2. Administration of Study Vaccine, Section 7.1. Safety Assessments and Procedures, Section 7.1.2. Safety Telephone Calls, Section 7.1.3. Safety Laboratory Assessments. Section 7.4. Exploratory Assessments, Section 7.6.1. Safety Review Committee, Section 8.1. Sample Size, Section 8.3.3.	Part B is being added to Study mRNA-1273-P304	To add a new study part (Part B) to continue to evaluate the benefit-risk profile of a booster dose of mRNA-1273.

Section # and Name	Description of Change	Brief Rationale
Immunogenicity Analyses, Section 8.4.1. Interim Analyses, APPENDIX 1: Schedule of Events, Table 10		
Section 3.1. General Design	Added a statement that the Part B Booster Phase may test or replace the prototype100 µg booster dose with a variant-specific mRNA-1273 vaccine.	To allow for flexibility in the protocol in case data show a decreased immune response.
Section 3.1.1. Study Periods	Added dose delay information for Part A.	To provide guidance to the investigators if the last dose is delayed.
Section 3.2. Scientific Rational for Study Design	Added Study mRNA-1273-P205.	To provide support of the booster dose.
Section 3.3. Justification for Dose and Choice of Study Population	Added Study mRNA-1273-P205.	To provide support of the booster dose.
Section 4.1.1.1. Inclusion Criteria for Transplant Recipients: Inclusion Criterion 1	Modified the time interval requirement between informed consent and date of transplant from 6 months to 90 days.	To provide opportunity for sites to enroll transplant recipients who are clinically eligible to receive the COVID-19 vaccine outside of the study.
Section 4.1.1.1. Inclusion Criteria for Transplant Recipients: Inclusion Criterion 1	Modified the time interval to be eligible at the time of consent after the second dose of Moderna COVID-19 vaccine from 2 months to 1 month.	For consistency with CDC guidance which states, “the additional dose of an mRNA COVID-19 vaccine should be administered at least 28 days after completion of the initial 2-dose mRNA COVID-19 primary vaccine series”.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1.1. Inclusion Criteria for Transplant Recipients: Inclusion Criterion 1	Added a statement that participants who received 2 doses of Moderna COVID-19 vaccine before transplant are not eligible.	To incorporate Clarification Memo 4 into the protocol.
Section 4.1.1.1. Inclusion Criteria for Transplant Recipients: Inclusion Criterion 2	Modified to specify that receipt of chronic immunosuppressive therapy for the prevention of allograft rejection be from 6 months to 90 days before signing consent.	For consistency with Inclusion Criterion 1.
Section 4.1.1.2. Exclusion Criteria for Transplant Recipients: Exclusion Criterion 4	Clarified that the exclusion criterion of prior or planned administration of a vaccine for SARS-CoV-2 is applicable to unvaccinated participants.	To incorporate Clarification Memo 3 into the protocol.
Section 4.1.1.2. Exclusion Criteria for Transplant Recipients: Exclusion Criterion 5	Clarified that the exclusion criterion of current administration of an investigational agent for COVID-19 is applicable to unvaccinated participants.	To incorporate Clarification Memo 3 into the protocol.
Section 4.1.1.2. Exclusion Criteria for Transplant Recipients: Exclusion Criterion 7	Modified the time interval between informed consent and history of biopsy-proven T-cell or Ab-mediated rejection from 6 months to 3 months.	For consistency with Inclusion Criterion 1.
Section 5.3.5. Study Vaccine Storage	Removed information that vials can be refrigerated for 30 days prior to use.	To align with the pharmacy manual.
Section 6.1.1. Individual Participant Criteria for Delay of Study Vaccination	Added “if possible or at a time the participant is clinically stable according to the judgement of the investigator” to the text describing rescheduling a visit.	To incorporate Clarification Memo 4 into the protocol.
Section 7.1.1 Use of Electronic Diaries	Updated the days for the safety telephone calls for previously vaccinated SOT recipients who receive dose 3.	To correct an error in the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1. Use of Electronic Diaries (as well as other sections such as SoE that cross-reference this change)	The language was clarified concerning the timing of eDiary prompts and safety calls when the last vaccine dose is delayed. If the last dose is delayed beyond the standard window, clinic visits will be adjusted based on if 2 dose or 3 dose regimens.	To incorporate Clarification Memo 5 into the protocol.
Section 7.1.2. Safety Telephone Calls	Added language regarding additional safety calls every 4 weeks should be scheduled when there is a gap beyond 28 days between the last safety call and the last study visit for Part A.	To incorporate Clarification Memo 5 into the protocol.
Section 7.3.1. Surveillance for COVID-19 Symptoms	Added safety phone call information for Part B participants.	To accommodate the new study part (Part B).
Section 7.10. Biomarkers	Added blood collection for biomarker analysis.	To accommodate the new study part (Part B).
Section 10.1. Appendix 1: Schedule of Events (Table 7 and Table 8)	Added a footnote for dose delay information.	To provide guidance to the investigators if the last dose is delayed.
Section 10.1. Appendix 1: Schedule of Events (Table 7, Table 8, and Table 9)	Removed the specific number of days since the most recent injection from below the eDiary and SC columns.	To align with other Sponsor protocols.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; mRNA = messenger RNA; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call; SOT = solid organ transplant.

IRB/IEC/Regulatory Authority/Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Regulatory Authority, as relevant.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273 for injection

Name of Active Ingredient: mRNA-1273

Protocol Title: A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls

Protocol Number: mRNA-1273-P304

Study Period (years): Approximately 1 year (~12 months for participants not receiving a booster dose, ~10 months for the single-dose plus booster dose regimen, ~10 months for 2-dose regimen plus booster dose regimen, ~13 months for 3-dose regimen plus booster dose, and ~6-months for booster dose regimen)

Phase of Development: Phase 3b

Estimated date first participant enrolled: Apr 2021

Estimated date last participant completed: May 2023

Total Number of Sites: ~20 US and non-US sites

Objectives and Endpoints

Objectives	Endpoints
Part A	
Primary Objectives	**Primary Endpoints**
• To evaluate the safety of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens	• Unsolicited adverse events (AEs) through 28 days after each injection • Medically attended adverse events (MAAEs) from Day 1 and throughout the study period • Serious adverse events (SAEs) from Day 1 and throughout the study period

	• Adverse events of special interest (AESIs), including myocarditis/pericarditis, from Day 1 and throughout the study period • AEs leading to discontinuation from dosing and/or study participation (withdrawal) from Day 1 and throughout the study period • Biopsy-proven organ rejection from Day 1 and throughout the study period
• To evaluate the reactogenicity of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimen	• Solicited local and systemic adverse reactions (ARs) through 7 days after each injection (for unvaccinated participants who received 2 doses of mRNA-1273) • Solicited local and systemic ARs through 7 days after each injection (for unvaccinated SOT recipients who received 3 doses and SOT recipients previously vaccinated outside the study who received a third dose)
• To evaluate serum neutralizing antibody (nAb) responses to doses of 100 µg mRNA-1273 obtained 28 days after the second dose or third dose	• The geometric mean titer (GMT) value of serum Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)-specific nAb level after the second dose (Day 57 for unvaccinated participants) • The GMT value of SARS-CoV-2-specific nAb level 28 days after dose 3 (Day 113 for unvaccinated SOT recipients and Day 29 for previously vaccinated SOT recipients)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to 2 or 3 doses of 100 µg mRNA-1273, as assessed by the level of anti-SARS-CoV-2 Spike (S) specific binding antibody (bAb) through 1 year after dose 2 or dose 3	• For all unvaccinated participants, the geometric mean (GM) value of anti-SARS-CoV-2 S-specific bAb on Day 1, Day 29 (28 days after dose 1), and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GM will be evaluated on Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) o For participants receiving the 3-dose regimen, GM will be evaluated on Day 85

	(dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GM will be evaluated on Day 1 (dose 3), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3) • For all unvaccinated participants, the geometric mean fold rise (GMFR) of bAb relative to Day 1 on Day 29 (28 days after dose 1), and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GMFR will evaluated on Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMFR will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GMFR of bAb relative to Day 1 (dose 3) will be evaluated on Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3)
• To evaluate the persistence of the immune response to 2 or 3 doses of 100 µg mRNA-1273, as assessed by the level of nAb through 1 year after dose 2 or dose 3	• For all unvaccinated participants, the GMT values of SARS-CoV-2-specific nAb on Day 1 and Day 29 (28 days after dose 1) o For participants in the 2-dose regimen, GMT will be evaluated on Day 209 (6 months after dose 2) and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMT will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3)

	• For all previously vaccinated SOT recipients, GMT values of SARS-CoV-2-specific nAb will be evaluated on Day 1 (dose 3), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3) • For all unvaccinated participants, GMFR of nAb relative to Day 1 will be evaluated on Day 29 (28 days after dose 1) and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GMFR will be evaluated on Day 209 (6 months after dose 2) and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMFR will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GMFR of nAb relative to Day 1 (dose 3) will be evaluated on Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3)
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult solid organ transplant (SOT) recipients and healthy adult participants with negative SARS-CoV-2 at baseline	• The incidence of asymptomatic SARS-CoV-2 infection among recipients of mRNA-1273 SARS-CoV-2 vaccine will be defined in participants with negative SARS-CoV-2 at baseline as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1, that becomes positive (as measured by Roche Elecsys) counted starting 28 days after the second dose and 28 days after the third dose of vaccine, OR • Positive reverse transcriptase polymerase chain reaction (RT-PCR) counted starting 14 days after the second and after the third dose of vaccine

• To describe the incidence of coronavirus disease 2019 (COVID-19) after vaccination with mRNA-1273 in SOT recipients and healthy participants	• First occurrence of COVID-19 starting 14 days after the second dose and after the third dose of vaccine, where COVID-19 is defined as symptomatic disease based on the following criteria • The participant must have experienced at least TWO of the following symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, or new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia, AND • The participant must have at least 1 nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR • First occurrence of severe COVID-19 starting 14 days after the second dose and after the third dose of vaccine, where severe COVID-19 is defined as symptomatic COVID-19 AND any of the following: o Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen saturation (SpO2) ≤ 93% on room air at sea level, or partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) < 300 mm Hg, OR o Respiratory failure or acute respiratory distress syndrome (ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation) or evidence of shock (systolic blood pressure [BP]

	< 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR o Significant acute renal, hepatic, or neurologic dysfunction, OR o Admission to an intensive care unit or death o The secondary case definition of COVID-19 is defined as the following symptoms: fever (temperature ≥ 38ºC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR
• To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine	• Safety laboratory assessments of kidney (serum creatinine, urine protein, and urine protein to creatinine ratio [UPCR]) and liver (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) function: o For unvaccinated SOT recipients, from Day 1 through Day 57 for SOT recipients who receive 2 doses and through Day 113 for SOT recipients who receive 3 doses of mRNA-1273 o For previously vaccinated SOT recipients, from Day 1 (dose 3) through Day 29 (28 days after dose 3)
• To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine	• Change in immunosuppressant medications to treat organ transplant rejection or to improve immune tolerance from Day 1 and throughout the study period. Change in immunosuppressant medication is defined as any of the following:

	○ any adjustments (temporarily or permanently) in immunosuppressants, ○ addition of new immunosuppressants, ○ or switching from 1 maintenance rejection prophylaxis regimen to another.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of genetic sequence of viral isolates with that of the vaccine sequence
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative immunoglobulin G [IgG]) and percent of study participants with 2×, 3×, and 4× rise of bAb relative to baseline
• To assess, in a subset of SOT recipients who received 3-dose regimen and healthy participants who received 2-dose regimen, SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T-cells as measured by flow cytometry at Day 1, Day 36, and Day 92 for unvaccinated participants, at Day 1 and Day 8 for previously vaccinated SOT recipients, and at Day 1 and Day 36 in healthy participants
• To define, in a subset of SOT recipients who received 3-dose regimen and healthy participants, the epitopes recognized by B-cells and antibodies generated in response to mRNA-1273	• Magnitude and phenotype of S protein-specific B-cells as measured by flow cytometry at Day 1, Day 36, and Day 92 for unvaccinated SOT recipients, at Day 1 and Day 8 for previously vaccinated SOT recipients, and at Day 1 and Day 36 in healthy participants • Determination of targeted major antigenic sites and amino acid residues on SARS-CoV-2 S protein
Part B – Booster Phase	

Primary Objectives	Primary Endpoints
• To evaluate the safety of the 100 µg BD of mRNA-1273	• Solicited local and systemic ARs through 7 days after BD injection • Unsolicited AEs through 28 days after BD injection • MAAEs throughout the study period • SAEs throughout the study period • AESIs, including myocarditis/pericarditis throughout the study period • AEs leading to discontinuation from dosing and/or study participation (withdrawal) throughout the study period • Biopsy-proven organ rejection throughout the study period
• To evaluate serum nAb responses elicited by the 100 µg mRNA-1273 obtained 28 days after the BD	• The GMT value of serum SARS-CoV-2-specific nAb level 28 days after the BD in SOT participants who received the Moderna primary series • The GMT value of SARS-CoV-2-specific nAb level 28 days after BD in SOT participants who received non-Moderna primary series
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the persistence of the immune response of the BD of mRNA 1273 vaccine (100 µg) as assessed by the level of SARS-CoV-2 S2P specific bAb through 6 months after BD	• The GM value of SARS-CoV-2 S2P specific bAb on BD-Day 1, BD-Day 29 (28 days after BD), BD-Day 181 (6 months after BD)
• To evaluate the persistence of the immune response of the BD of mRNA-1273 vaccine (100 µg) as assessed by the level of nAb through 6 months after BD	• The GM values of SARS-CoV-2-specific nAb on BD-Day 1, BD-Day 29 (28 days after BD), BD-Day 181 (6 months after BD)

• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult solid SOT recipients and healthy adult participants with negative SARS-CoV-2 at baseline	• The incidence of asymptomatic SARS-CoV-2 infection among recipients of mRNA-1273 SARS-CoV-2 vaccine will be defined in participants with negative SARS-CoV-2 at baseline as: o bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1, that becomes positive (as measured by Roche Elecsys) counted starting 28 days after the BD, OR o Positive RT-PCR counted starting 14 days after the BD
• To describe the incidence of COVID-19 after vaccination with mRNA-1273 in SOT recipients and healthy participants	• First occurrence of COVID-19 starting 14 days after BD of vaccine, where COVID-19 is defined as symptomatic disease based on the following criteria • The participant must have experienced at least TWO of the following symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, or new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia, AND • The participant must have at least 1 nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR • First occurrence of severe COVID-19 starting 14 days after the BD of vaccine, where severe COVID-19 is defined as symptomatic COVID-19 AND any of the following: o Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen

	saturation (SpO2) ≤ 93% on room air at sea level, or partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) < 300 mm Hg, OR o Respiratory failure or acute respiratory distress syndrome (ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation) or evidence of shock (systolic blood pressure [BP] < 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR o Significant acute renal, hepatic, or neurologic dysfunction, OR o Admission to an intensive care unit or death. • The secondary case definition of COVID-19 is defined as the following symptoms: fever (temperature ≥ 38ºC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR
• To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine	• Safety laboratory assessments of kidney (serum creatinine, urine protein, and UPCR) and liver (ALT, AST, ALP, and bilirubin) function from BD-D1 through BD-D29 (28 days after BD)
• To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine	• Change in immunosuppressant medications to treat organ transplant rejection or to improve immune tolerance from BD-D1 and throughout the study period. Change in immunosuppressant medication is defined as any of the following:

	○ any adjustments (temporarily or permanently) in immunosuppressants, ○ addition of new immunosuppressants, ○ or switching from 1 maintenance rejection prophylaxis regimen to another
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of genetic sequence of viral isolates with that of the vaccine sequence
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and percent of study participants with 2×, 3×, and 4× rise of bAb relative to baseline
• To assess, in a subset of SOT recipients and healthy participants who received BD, SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T-cells BD-D1 and BD-D8
• To define, in a subset of SOT recipients and healthy participants, the epitopes recognized by B-cells and antibodies generated in response to mRNA-1273	• Magnitude and phenotype of S protein-specific B-cells as measured by flow cytometry at BD-D1 and BD-D8 • Determination of targeted major antigenic sites and amino acid residues on SARS-CoV-2 S protein

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = adverse reaction; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; bAb = binding antibody; BD = booster dose; BP = blood pressure; COVID-19 = coronavirus disease 2019; D = day; FIO2 = fraction of inspired oxygen; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = Nasopharyngeal; PaO2 = partial pressure of oxygen; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = SARS-CoV-2 spike protein modified with 2 proline substitutions to stabilize the spike protein in a prefusion conformation; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SOT = solid organ transplant; SpO2 = oxygen saturation; UPCR = urine protein to creatinine ratio.

Overall Study Design:

This is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in SOT recipients and healthy controls. Adult kidney and liver transplant recipients and healthy control participants who are at least 18 years of age will be enrolled.

Approximately 240 adult participants (220 previously vaccinated or unvaccinated who have had a kidney or liver transplant and 20 unvaccinated healthy adults) will be enrolled. At least 50 SOT recipients who completed primary vaccination series with a non-Moderna COVID-19 vaccine under Emergency Use Authorization (EUA) (outside of the mRNA-1273-P304 study) will be enrolled in Part B.

In Part A, all SOT recipients who were unvaccinated prior to enrollment will receive 2 doses of 100 µg of mRNA-1273 28 days apart (window of -3/+7 days for the second dose) (Group A1). The SOT recipients will be offered the opportunity to receive a third primary dose of mRNA-1273 at Day 85 (window of -3/+7 days for the third dose) as per the EUA Fact Sheet available at the time of protocol finalization (Group A2). All healthy participants will receive 2 doses of 100 µg of mRNA-1273 28 days apart (window of -3/+7 days for the second dose) (Group A5). The SOT recipients who were previously vaccinated with 2 doses of Moderna COVID-19 vaccine under the EUA prior to enrollment will receive dose 3 on Day 1 (Group A3). These participants will be referred to as "previously vaccinated" throughout this document. Under Amendment #4, unvaccinated SOT participants who will be enrolled will be given 3 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose. Under Amendment #4, SOT participants previously vaccinated with 2 doses of Moderna COVID-19 vaccine outside of the study who will be enrolled will receive a third 100 µg dose in Part A then proceed to Part B to receive a 100 µg BD.

In Part B, all participants in Part A will be offered a 100 µg BD of mRNA-1273 at least 4 months from the last dose. SOT recipients who completed primary COVID-19 vaccination series under EUA will receive a 100 µg BD on BD-D1 (Group B4).

Study Arm	Part A	Doses in P304 Part A	Part A Dose	Move on to Part B?	Part B	Doses in P304 Part B	Part B B-Dose	Total Doses in P304
SOT Recipient Cohorts								
Unvaccinated participants who consent to receive only 2 doses in Part A (Days 1 and 29)	**Group A1**	2	100 µg		NA	N/A	N/A	2
Unvaccinated participants who consent to receive 3 doses in Part A (Days 1, 29, and 85)	**Group A2**	3	100 µg	➡	**Group B2**	1	100 µg	4
Participants previously vaccinated with 2 doses of the Moderna COVID-19 vaccine under the EUA who consent to receive a third dose in Part A (Day 1)	**Group A3**	1	100 µg	➡	**Group B3**	1	100 µg	2
SOT recipients who completed primary vaccination with an mRNA or non-mRNA COVID-19 vaccine outside mRNA-1273-P304 who consent to receive 1 booster dose (in Part B)	N/A	N/A	N/A		**Group B4**	1	100 µg	1

Healthy Adult Cohort								
Healthy adults who consent to receive 2 doses in Part A (Days 1 and 29)	**Group A5**	2	100 µg	→	**Group B5**	1	100 µg	3

Abbreviations: B-Dose = booster dose; EUA = Emergency Use Authorization; SOT = solid organ transplant

For Part A, the primary immunogenicity goal of the study is to evaluate serum antibody (Ab) responses obtained 28 days after the third dose (Day 113 for unvaccinated SOT participants who receive the 3-dose regimen and Day 29 for previously vaccinated SOT participants) of mRNA-1273 in SOT recipients. Using the Ab threshold established from Study P301 (if available at the time of database lock), an additional exploratory analysis will be performed by measuring the proportion of participants with a serum Ab level at Day 57 for unvaccinated participants of 2-dose regimen), Day 113 (unvaccinated SOT recipients of the 3-dose regimen), and Day 29 (previously vaccinated SOT recipients who receive dose 3) greater than or equal to the Ab threshold of protection against COVID-19, with a 2 sided 95% CI using the Clopper Pearson method by cohort arm.

This study will monitor participants for a total of up to 12 months (12 months after the last dose of the vaccine for participants not receiving a BD or 6 months after their BD). The SOT participants who do not consent to receive a third dose of mRNA-1273 and healthy adult participants will be monitored for a total of 12 months after their second dose. Safety assessments will include solicited local and systemic adverse reactions (ARs) for 7 days after each dose; unsolicited AEs for 28 days after each dose; MAAEs; SAEs; AESIs; AEs leading to discontinuation from dosing and/or study participation (withdrawal) from dose 1 through the end of study; concomitant medications associated with AEs, MAAEs, or COVID-19 or SARS-CoV-2 infection; participant experience of COVID-19 symptoms; biopsy-proven organ rejection; safety laboratory assessments; vital sign measurements; and physical examination findings as presented in the applicable schedule of events (SoE).

From all unvaccinated SOT participants who receive 3 doses of mRNA-1273 (Group A2), blood samples will be collected at baseline (Day 1), Day 29 (28 days after dose 1), Day 57 (28 days after dose 2), Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (12 months after dose 3).

From unvaccinated participants who receive 2 doses of mRNA-1273 (healthy adults [Group A5] and SOT recipients who decline to receive a third dose [Group A1]), blood samples will be

collected at baseline (Day 1), Day 29 (28 days after dose 1), Day 57 (28 days after dose 2), Day 209 (6 months after dose 2), and Day 394 (12 months after dose 2).

From previously vaccinated SOT participants who receive dose 3 of mRNA-1273 (Group A3), blood samples will be collected at pre-dose 3 (Day 1), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (12 months after dose 3) for assessment of the following endpoints and analytes:

- Measurement of SARS-CoV-2-specific bAb and nAb responses
- Development of Ab directed against nonvaccine antigen (nucleocapsid protein), which will signify infection with SARS-CoV-2. Participants who tested positive for Ab against SARS-CoV-2 nucleocapsid protein at baseline can continue in the study.

From unvaccinated participants, blood samples for cell-mediated immunity (CMI) studies will also be collected at Day 1, Day 36, and Day 92 (SOT recipients receiving 3 doses [Group A2]) from a subset of up to 50 SOT participants, as well as, from 20 healthy controls (Group A5) (Day 1 and Day 36), and from a subset of at least 50 previously vaccinated SOT recipients (Group A3) at Day 1 and Day 8 for exploratory assessments to characterize T- and B-cell responses to vaccine.

The NP swab samples obtained at illness visits will be used as sources of SARS-CoV-2 for genetic sequencing.

SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) will also be collected at Illness and Convalescent visits.

The number of cases of COVID-19 will be assessed throughout the study. Once a participant is identified as a case of COVID-19, a convalescent visit will be scheduled approximately 28 days after the confirmed diagnosis for a clinical evaluation and immunologic assessment of SARS-CoV-2 infection.

For unvaccinated SOT recipients (Group A1 and Group A2), laboratory assessments for safety related to kidney function for kidney SOT recipients (serum creatinine, urine protein, and UPCR) and liver function for liver SOT recipients (ALT, AST, ALP, and bilirubin) will be monitored on Day 1, Day 8, Day 29, Day 36, and Day 57 for SOT recipients who receive 2 doses only (Group A1) and on additional Day 85, Day 92, and Day 113 for SOT recipients who receive 3 doses (Group A2).

For previously vaccinated SOT recipients (Group A3), laboratory assessments for safety will be monitored on Day 1 (dose 3), Day 8, and Day 29.

After Day 57 (for unvaccinated SOT participants who receive 2 doses [Group A1]) or after Day 113 (for unvaccinated SOT participants who receive 3 doses [Group A2]) or after Day 29 (for previously vaccinated SOT recipients who receive a 1 dose (dose 3) of mRNA-1273 [Group A3]), the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

Part B – Booster Phase

Part B is designed to offer participants in Part A, who are at least 4 months from the last dose, the option to receive a BD (100 µg) of the prototype mRNA-1273 vaccine (Group B2, Group B3, and Group B5). Part B is also designed to enroll SOT participants who completed primary vaccination series with mRNA or non-mRNA COVID-19 vaccine under the EUA who are at least 4 months from last dose. At least 50 SOT recipients who completed primary vaccination series with a non-Moderna COVID-19 vaccine under the EUA (outside of the mRNA-1273-P304 study) will be enrolled in Part B. In case a variant of concern emerges and available data show a decreased immune response after vaccination with the prototype 100 µg BD, the Part B Booster Phase may test or replace the prototype 100 µg BD with a variant-specific mRNA-1273 vaccine (ie, Omicron-specific or mRNA-1273.529).

Primary Series Vaccine	**Primary Series Number of Doses**
mRNA COVID-19 vaccine (ie. Moderna, Pfizer)	3 doses
non-mRNA COVID-19 vaccine (ie. Janssen)	2 doses or at least 1 dose combined with an mRNA COVID-19 vaccine

If eligible, each study participant in Part A will receive a notification letter and will be asked to schedule a BD-1 visit at their study site. Principal Investigators should consider current local public health guidance for administration of COVID-19 vaccines under EUA and marketing authorization (if any) when determining the scheduling priority of participants.

At the BD-1 visit, each participant will:

- Each study participant in Part A will be encouraged to remain in the ongoing study,
- Sign a revised informed consent form (ICF) that includes both updated safety information relevant to the ongoing study and a BD.
    - Active participants from Part A will be offered the option to receive a 100 µg BD (Group A5, Group B2 and Group B3),

  - Eligible SOT participants who completed the primary vaccination series under EUA will be given a 100 µg BD of mRNA-1273 (Group B4),
  - Under Amendment #4, unvaccinated SOT participants who will be enrolled will be given 3 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose.
  - Under Amendment #4, SOT participants previously vaccinated with 2 doses of Moderna COVID-19 vaccine outside of the study who will be enrolled will receive a third 100 µg dose in Part A then proceed to Part B to receive a 100 µg BD.

- Be counselled about the importance of continuing other public health measures to limit the spread of disease including social distancing, wearing a mask, and hand-washing.

At the BD-1 visit, participants will have the following study site visits and complete scheduled activities according to the Part B SoE:

- BD-1 visit: Participants will receive a single 100 µg dose of mRNA-1273
- BD-1a visit: Day 4, 3 days after BD on Day 1
- BD-2 visit: Day 8, 7 days after BD on Day 1
- BD-3 visit: Day 29, 28 days after the BD on Day 1
- BD-4 visit: Day 181, 180 days after the BD on Day 1

Study Periods

There will be 3 study periods: a Screening Period, a Treatment Period, and a Follow-up Period.

For unvaccinated participants (SOT and healthy) who receive the 2-dose vaccine regimen in Part A (Group A1 and Group A5):

The study comprises 8 scheduled visits, including a screening visit and 7 scheduled clinic visits. Electronic diary (eDiary) recording of solicited local and systemic reactogenicity will occur on the day of each injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363. Additional safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377. If the last dose is delayed, additional safety calls every 4 weeks should be scheduled when the gap between the safety call scheduled on D377 and the last study visit is beyond 28 days.

Per participant, the study duration will be approximately 13 months, which includes 1 week for screening (Day -7 to Day 1), 28 days for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. Day 0 and Day 1 may be combined on the same day.

For unvaccinated SOT participants who receive the 3-dose vaccine regimen in Part A (Group A2):

The study comprises 11 scheduled visits, including a screening visit and 10 scheduled clinic visits. The eDiary recording of solicited local and systemic reactogenicity will occur on the day of each injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 127 to Day 239 and again from Day 279 to Day 419. Additional safety follow-up via a safety telephone call will be performed every 4 weeks from Day 141 to Day 253 and again from Day 293 to Day 433. If the last dose is delayed, additional safety calls every 4 weeks should be scheduled when the gap between the safety call scheduled on D433 and the last study visit is beyond 28 days.

Per participant, the study duration will be approximately 15 months, which includes 1 week for screening (Day -7 to Day 1), 3 months for dosing (on Day 1, Day 29, and Day 85), and 12 months of follow-up after the third dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. Day 0 and Day 1 may be combined on the same day.

For previously vaccinated SOT participants who receive the single-dose vaccination regimen (dose 3) in Part A (Group A3):

The study comprises 6 scheduled visits, including a screening visit and 5 scheduled clinic visits. eDiary recording of solicited local and systemic reactogenicity (Section 7.5.3) will occur on the day of injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 43 to Day 155 and again from Day 194 to Day 306. Additional safety follow-up via a safety telephone call will be performed every 4 weeks from Day 57 to Day 169 and again from Day 208 to Day 320.

Per participant, the study duration will be approximately 12 months, which includes 1 week for screening (Day -7 to Day 1), and 12 months of follow-up after dose 3 to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. The screening visit and Day 1 may be combined on the same day (Table 9).

For participants who receive the BD in Part B (Group B2, Group B3, Group B4, and Group B5):

The study comprises 5 scheduled clinic visits and 6 safety calls (BD-D15, BD-D22, BD-D59, BD-D89, BD-D119, and BD-D149).

Per healthy participant receiving 2 mRNA-1273 doses in Part A who consent to receive a BD (Group B5), the study duration will be approximately 10 months, which includes 1 week for screening (Day -7 to Day 1), 4 months for dosing (on Day 1, Day 29, and Day 129 for BD), and 6 months of follow-up after the BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who received the 3 mRNA-1273 doses in Part A (Group B2) who consent to receive a BD, the study duration will be approximately 13 months which includes 1 week for screening (Day -7 to Day 1), approximately 7 months of dosing (on Day 1, Day 29, Day 85, and Day 205 for BD) and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who previously received 2 doses under EUA, enrolled in Part A to receive a third dose (Group B3) and who consent to receive a BD, the study duration will be approximately 10 months which includes 1 week for screening (Day -7 to Day 1), 4 months of dosing (Day 1 [dose 3] and Day 120 [BD]) and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who previously completed primary vaccination series (3 doses) under EUA (Group B4) who consent to receive a BD, the study duration will be approximately 6 months which includes 1 week for screening (Day -7 to Day 1), 1 day for dosing and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

This study will be conducted in compliance with the protocol, Good Clinical Practice, and all applicable regulatory requirements.

Screening Period

The Screening Period for each participant starts with the first screening visit (Day 0) and ends with the Day 1 visit. The Screening Period can last up to 7 days. After signing the ICF, participants will undergo screening assessments to determine study eligibility. The investigator will review study entry criteria to determine the participant eligibility during the Screening Period.

Participants deemed eligible will enter the Treatment Period.

Treatment Period and Follow-up Period

The Treatment Period for each participant starts with Day 1 and is scheduled to end 28 days after each dose of vaccine. In Part A, for unvaccinated SOT and healthy participants who receive the 2-dose regimen (Group A1 and A5), the Follow-up Period starts with Day 58 and is scheduled to end on Day 394 (12 months after the second dose). The Follow-up Period for unvaccinated SOT participants who receive the 3-dose regimen (Group A2) starts with Day 114 and is scheduled to end on Day 450 (12 months after the third dose). The Follow-up Period for previously vaccinated participants (Group A3) starts with Day 29 and is scheduled to end on Day 365 (12 months after dose 3). In Part B (Group B2, Group B3, Group B4, and Group B5), Follow-up Period starts with Day 29 and is scheduled to end on BD-D181 (6 months after BD).

For Part A: On Day 1, after the completion of the scheduled assessments, all participants will be administered a single intramuscular (IM) dose of 100 µg of mRNA-1273. Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. For unvaccinated SOT and healthy participants (Group A1, Group A2, and Group A5), the second dose of vaccine will be administered on Day 29. Unvaccinated SOT recipients who consent to receive a third dose of vaccine (Group A2) will receive it on Day 85. Previously vaccinated SOT recipients (Group A3) will receive dose 3 on Day 1. Participants will be monitored for 12 months after the second and third dose (as applicable) of vaccine for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

For Part B (Group B2, Group B3, Group B4, and Group B5): On BD-D1, after the completion of the scheduled assessments, at least 4 months after the last dose, all participants will be administered a single IM dose of 100 µg BD of mRNA-1273. Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. Participants will be monitored for 6 months after the BD for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Scheduled testing for the presence of SARS-CoV-2 by RT-PCR will occur after collecting NP swab samples on each day of injection: in Part A, on Day 1, Day 29, and Day 85 before dosing as well as on Day 57 (28 days after the second dose for unvaccinated SOT and healthy participants [Group A1 Group A2, and Group A5]) and Day 113 (28 days after the third dose for unvaccinated SOT recipients [Group A2]); and Day 29 (for previously vaccinated SOT recipients [Group A3]), and in Part B (Group B2, Group B3, Group B4, and Group B5), on BD-D1 before dosing. During the Treatment Period and Follow-up Period, participants who meet prespecified disease criteria that suggest possible SARS-CoV-2 infection, will be asked to contact the study site to arrange for a prompt and thorough assessment, including an NP swab

sample to be tested for the presence of SARS-CoV-2 by RT-PCR. Confirmed, symptomatic cases of SARS-CoV-2 infection will be captured as MAAEs.

Blood samples for immunogenicity assessment:

All participants will be monitored for safety and reactogenicity and provide pre- and post-dose blood specimens for immunogenicity through 12 months after additional primary dose (dose 3 [Group A3]) and second (Group A1) and third (Group A2) (as applicable) doses of mRNA-1273 (Part A) and through 6 months after BD (Group B2, Group B3, Group B4, and Group B5). Blood sampling for immunogenicity testing is scheduled throughout the study:

- For unvaccinated SOT and healthy participants who receive the 2-dose regimen, on Days 1 and 29, as well as 28 days and 6 and 12 months after the second dose (Part A, Group A1 and Group A5),
- For unvaccinated SOT participants who receive the 3-dose regimen, on Days 1, 29, 57, and 85, as well as 28 days and 6 and 12 months after the third dose (Part A, Group A2),
- For previously vaccinated SOT participants who receive dose 3, on Days 1 and 29 (28 days after dose 3), as well as 6 and 12 months after dose 3 (Part A, Group A3).
- For participants in Part B (participants in Part A who consented to receive a BD [Group B2, Group B3, and Group B5] and SOT participants who completed the primary vaccination series with any COVID-19 vaccine under EUA who receive a BD [Group B4]), on BD-D1, BD-D29, and BD-D181

Blood samples for CMI Analysis:

<u>Part A</u>

For unvaccinated SOT participants (Group A1 and Group A2), blood samples will also be collected for CMI analysis at Day 1, Day 36, and Day 92 (SOT recipients who receive a third dose [Group A2]) from a subset of up to 50 SOT recipients, as well as, from 20 healthy controls (Group A5) at Day 1 and Day 36.

Blood samples will also be collected from a subset of at least 50 previously vaccinated SOT recipients (Group A3) for CMI analysis at Day 1 (dose 3) and Day 8 (7 days after dose 3).

<u>Part B</u>

For participants in Part B (participants in Part A who consented to receive a BD [Group B2, Group B3, and Group B5] and SOT participants who completed the primary vaccination series under EUA who receive a BD [Group B4]), blood samples will be collected for CMI analysis at BD-D1 and BD-D8 (7 days after BD)

Blood and urine samples for kidney and liver function:

Blood and urine samples related to kidney (for kidney SOT) and liver function (for liver SOT) will be monitored:

Part A

- On Day 1, Day 8, Day 29, Day 36, and Day 57 for unvaccinated SOT participants who receive 2 doses only (Group A1) and on additional Days 85, 92, and 113 for unvaccinated SOT recipients receiving 3 doses (Group A2).
- On Day 1 (dose 3), Day 8, and Day 29 for previously vaccinated SOT recipients (Group A3).
- After Day 57 (for unvaccinated SOT recipients receiving 2 doses [Group A1]) or after Day 113 (for unvaccinated SOT recipients receiving 3 doses [Group A2]), or after Day 29 (for previously vaccinated SOT recipients receiving 1 dose of mRNA-1273 [Group A3]), the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

Part B

- On BD-D1, BD-D8, and BD-D29 for SOT participants (Group B2, Group B3, and Group B4): After Day 29, the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

Blood samples for biomarker analysis:

During BD-D4 (Part B of the study [Group B2, Group B3, Group B4], and Group B5), participants who chose to receive a BD will have blood draws (biomarker plasma and biomarker serum samples) which will be stored for potential future biomarker assessment.

Participants will be instructed on the day of the first dose and reminded on the days of the second, third, and fourth doses (as applicable) how to document and report solicited local or systemic ARs in a provided eDiary. Solicited ARs, unsolicited AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), or biopsy-proven organ rejection will be assessed according to the time points in the applicable SoE.

Participants may experience or report an AE that necessitates an unscheduled visit. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being

of the participant during the study at the investigator's discretion. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

Safety Oversight:

The contract research organization's medical monitor, the Sponsor's medical monitor, and the individual study site investigator(s) will monitor safety throughout the study.

An independent safety review committee (SRC) consisting of transplant nephrologist(s) and hepatologist(s) not involved in the conduct of the study will monitor and adjudicate for events of organ transplant rejection starting after the first dose on Day 1 and throughout the study period. The SRC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SRC. Details regarding the SRC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

An independent cardiac event adjudication committee (CEAC) that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet Centers for Disease Control and Prevention (CDC) criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, which will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants or potential study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

In addition, an Internal Safety Team (IST) will be created specifically to review safety and reactogenicity data after:

- At least 10 SOT recipients have received their third dose of study vaccine (Group A2 and Group A3) and have at least 7 days of reactogenicity data
- At least 55 SOT recipients have received their third dose of study vaccine (Group A2 and Group A3), unless a safety event requires earlier review
- Any other ad hoc safety concerns based on ongoing safety surveillance

The IST will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the IST. Details regarding the IST composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

Study Duration:

Part A:

Per participant receiving 2 vaccine doses (Group A1), the study duration will be approximately 13 months, which includes 1 week for screening, 1 month for dosing, and 12 months of follow-up after the second dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per participant receiving 3 vaccine doses (Group A2), the study duration will be approximately 15 months, which includes 1 week for screening, 3 months for dosing, and 12 months of follow-up after the third dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per participant receiving 1 vaccine dose only (dose 3) (Group A3), the study duration will be approximately 12 months, which includes 1 week for screening, 1 day for dosing, and 12 months of follow-up after dose 3 to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Part B – Booster Phase

Per healthy participant receiving 2 doses of mRNA-1273 in Part A (Group B5), the study duration will be approximately 10 months, which includes 1 week for screening (Day -7 to Day 1), 6 months for dosing (on Day 1, Day 29, and Day 129 for BD), and 6 months of follow-up after the BD to monitor for safety, immunogenicity, and breakthrough SARSCoV2 infection or COVID-19.

Per SOT study participant receiving 3 doses of mRNA-1273 in Part A (Group B2), the study duration will be approximately 13 months which includes 1 week for screening (Day -7 to Day 1), approximately 9 months of dosing (on Day 1, Day 29, Day 85, and Day 205 for BD) and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who previously completed primary vaccination series (3 doses) under EUA (Group B4), the study duration will be approximately 6 months which includes 1 week for screening (Day -7 to Day 1), 1 day for dosing and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Number of Participants:

Approximately 240 participants (220 unvaccinated and previously vaccinated SOT recipients and 20 unvaccinated healthy controls) will be enrolled in the study. At least 50 SOT recipients

who completed primary vaccination series with a non-Moderna COVID-19 vaccine under EUA (outside of the mRNA-1273-P304 study) will be enrolled in Part B.

Study Eligibility Criteria (Part A):

Eligibility Criteria for Transplant Recipients (Group A1, Group A2, and Group A3):

Inclusion Criteria for Transplant Recipients:

Each participant must meet all of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent (Day 0), is EITHER a kidney or a liver (single organ) transplant recipient who is at least 90 days after transplantation at the time of consent, and is EITHER:

a. Unvaccinated, or

b. Previously vaccinated with 2 doses of Moderna COVID-19 vaccine who is at least 1 month after the second dose at the time of consent. Participants who received the 2 doses of Moderna COVID-19 vaccine before transplant are not eligible

2. Received chronic immunosuppressive therapy for the prevention of allograft rejection for a minimum of 90 days before signing consent, including but not limited to: glucocorticoids (eg, prednisolone), immunophilin binding agents (eg, calcineurin inhibitors, mTOR inhibitors), or inhibitors of de novo nucleotide synthesis (eg, mycophenolic acid, mizoribine, leflunomide, azathioprine).

3. Understands, agrees, and is able to comply with the study procedures and provides written informed consent.

4. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

   - Has a negative pregnancy test at Screening and on the day of the first dose (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).
   - Has agreed to continue adequate contraception through 3 months following the second dose (Day 29) for those receiving 2-dose regimen, through 3 months following the third dose (Day 85) for those receiving 3-dose regimen, and through

3 months following the third dose (Day 1) for those previously vaccinated SOT recipients.

- Is not currently breastfeeding.

See Section 10.3, Appendix 3 for Contraceptive Guidance.

5. Is medically stable, according to investigator's judgement, during the 3 months before signing consent. Medically stable is defined as having no significant worsening of a medical condition requiring medical intervention (eg, hospitalization, change in medical therapy).

Exclusion Criteria for Transplant Recipients

Participants who meet any of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration or any known history of SARS-CoV-2 infection or positive SARS-CoV-2 test.
2. Is pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the screening visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Has prior or planned administration of a coronavirus vaccine (eg, SARS-CoV-2 [for unvaccinated participants only], SARS-CoV, or MERS [Middle East Respiratory Syndrome] -CoV vaccine).
5. Has current treatment with investigational agents for either prophylaxis against COVID-19 (for unvaccinated participants only) or treatment of COVID-19 (eg, anti-SARS-CoV-2 monoclonal antibodies).
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - A history of more than 1 solid organ transplanted (eg, kidney and pancreas). A history of previous kidney or liver transplant is acceptable.

- A history of clinically relevant donor-specific Ab.
- A history of complications of immunosuppression; for example, the following:
  - Hypogammaglobulinemia and post-transplant lymphoproliferative disorders
  - Cytomegalovirus viremia or BK viremia within 1 month of informed consent
- Active infection at the time of consent
- A history of biopsy-proven T-cell or Ab-mediated rejection within 3 months of informed consent, or suspected active or chronic rejection according to the investigator's judgment
- Suspected clinically relevant active hepatitis, including viral hepatitis, according to the investigator's judgment
- Bleeding disorder that is considered a contraindication to IM injection or phlebotomy
- Dermatologic conditions that could affect local solicited AR assessments
- Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients
- Known human immunodeficiency virus infection

8. Has received:
   - Any nonstudy vaccine within 28 days before or after any dose of vaccine (except for seasonal influenza vaccine, which is not permitted within 14 days before or after any dose of vaccine)
   - Intravenous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to Day 1
   - Therapies that have depleting properties on T-cells, B-cells, and plasma cells (examples of depletional therapies include, but are not limited to, antithymocyte globulin, monoclonal antibodies, and proteosome inhibitors) within the last 3 months prior to enrollment
9. Participated in an interventional clinical study within 28 days prior to Day 0 or plans to donate blood products while participating in this study.
10. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

Eligibility Criteria for Healthy Adults (Group A5):

Inclusion Criteria for Healthy Adults:

Each participant must meet all of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent (Day 0), and is in good general health without current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition, according to investigator assessment, at the time of consent, and has not been vaccinated with any COVID-19 vaccine at the time of consent.
2. Understands, agrees, and is able to comply with the study procedures and provides written informed consent.
3. 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 Screening and on the day of the first dose (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)
    - Has agreed to continue adequate contraception through 3 months following the second dose (Day 29)
    - Is not currently breastfeeding

See Section 10.3, Appendix 3 for Contraceptive Guidance.

4. Is medically stable, according to investigator's judgment, during the 3 months before signing consent. Medically stable is defined as having no significant worsening of a medical condition requiring medical intervention (eg, hospitalization, change in medical therapy).

Exclusion Criteria for Healthy Adults:

Participants who meet any of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration or any known history of SARS-CoV-2 infection or SARS-CoV-2 test.

2. Is pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the screening visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Has prior or planned administration of a coronavirus vaccine (eg, SARS-CoV-2, SARS-CoV, or MERS-CoV vaccine).
5. Has current treatment with investigational agents for either prophylaxis against COVID-19 or treatment of COVID-19 (eg, anti-SARS-CoV-2 monoclonal antibodies).
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Active infection at the time of consent
    - Bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments
    - Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients
    - Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition
8. Has received:
    - Any nonstudy vaccine within 28 days before or after any dose of vaccine (except for seasonal influenza vaccine, which is not permitted within 14 days before or after any dose of vaccine)
    - Intravenous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to Day 1
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent)

9. Participated in an interventional clinical study within 28 days prior to Day 0 or plans to donate blood products while participating in this study.
10. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

Study Eligibility Criteria (Part B):

Inclusion Criteria (Group B2, Group B3, Group B4, and Group B5)

1. a. Participants must have been previously enrolled in the mRNA-1273-P304 study, are actively participating in Part A and are at least 4 months from the last dose, or

   b. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent, is EITHER a kidney or a liver (single organ) transplant recipient who is at least 90 days after transplantation at the time of consent AND who completed primary vaccination series (3 doses for mRNA COVID-19 vaccine; 2 doses for non-mRNA COVID-19 vaccine or at least 1 dose of non-mRNA combined with 1 dose of mRNA COVID-19 vaccine) under the EUA who are at least 4 months from the last dose. All primary COVID-19 vaccination series must be completed after transplant.
2. Female participants of childbearing potential may be enrolled in the study if the participant has a negative pregnancy test on the day of the booster dose injection (BD-Day 1).

Exclusion Criteria (for participants who completed primary vaccination series under EUA) (Group B4)

Exclusion Criteria in Part A will apply except prior or planned administration of a coronavirus vaccine and current treatment with investigational agents for either prophylaxis against COVID-19.

Study Treatments:

Investigational Product:

The investigational product (mRNA-1273 vaccine) is a lipid nanoparticle (LNP) dispersion of a messenger RNA (mRNA) encoding the prefusion stabilized spike (S) protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102 (heptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine; and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000. mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white

dispersion in appearance, at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

Mode of Administration:

Doses will be administered by IM injection into the deltoid muscle according to the procedures specified in the mRNA-1273-P304 Pharmacy Manual. Preferably, all doses should be administered into the same nondominant arm for each dose. Neither dose should be administered into an arm that contains an arteriovenous fistula.

Procedures and Assessments:

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant, according to the applicable SoE:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using the eDiary
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days)
- MAAEs throughout the study period
- SAEs throughout the study period
- AESIs throughout the study period
- AEs leading to discontinuation from dosing and/or study participation (withdrawal) throughout the study period
- Biopsy-proven organ rejection throughout the study period. A biopsy report will be needed for documentation
- Safety laboratory assessments:

  Part A

  – For unvaccinated SOT recipients who receive the 2-dose regimen (Group A1), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, Day 29, Day 36, and Day 57. After Day 57, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and

suspected or confirmed events of organ transplant rejection until the end of study.

– For unvaccinated SOT recipients who receive the 3-dose regimen (Group A2), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, Day 29, Day 36, Day 57, Day 85, Day 92, and Day 113. After Day 113, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

– For previously vaccinated SOT recipients who receive dose 3 (Group A3), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, and Day 29. After Day 29, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

Part B

- For SOT participants who completed primary vaccination series (Group B2, Group B3, and Group B4), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on BD-D1, BD-D8, and BD-D29. After BD-D29, the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

- Vital sign measurements
- Physical examination findings
- 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 treatment and until the end of their participation in the study
- Changes in immunosuppressant medications in SOT recipients

Safety Procedures:

The eDiary will be used throughout the study as specified in the applicable SoE. The eDiary will be the only source documents allowed for solicited local or systemic ARs. In Part A, the eDiary will also be used every 4 weeks to capture the occurrence of AEs, MAAEs, SAEs, AESIs, or AEs leading to discontinuation from dosing and/or study participation (withdrawal) as follows:

- Starting at Day 71 through Day 183 and again starting at Day 223 through Day 363 for unvaccinated SOT and healthy participants of 2 vaccine doses (Group A1 and Group A5),
- Starting at Day 127 through Day 239 and again starting at Day 279 through Day 419 for unvaccinated SOT recipients of 3 vaccine doses (Group A2), and
- Starting at Day 43 through Day 155 and again starting at Day 194 through Day 306 for previously vaccinated SOT recipients who receive dose 3 (Group A3).

In Part A, safety telephone calls will be used every 4 weeks to collect information as specified in the applicable SoE about occurrence of AEs, MAAEs (including biopsy-proven organ rejection), SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.5.8). In addition, study personnel will collect information on known participant close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms:

- From Day 85 through Day 197 and again from Day 237 through Day 377 for unvaccinated SOT and healthy participants of 2 vaccine doses (Group A1 and Group A5);
- From Day 141 through Day 253 and again starting at Day 293 through Day 433 for unvaccinated SOT recipients of 3 vaccine doses (Group A2);
- Starting at Day 57 through Day 169 and again starting at Day 208 through Day 320 for previously vaccinated SOT recipients who receive dose 3 (Group A3).

The timing of eDiary prompts for safety follow-ups and safety calls will not be adjusted if the last dose is delayed. Additional safety calls every 4 weeks should be scheduled if there is a gap beyond 28 days between the safety call scheduled on D377 (for 2 doses [Group A1 and Group A5]) or D433 (for 3 doses [Group A2]) and the last study visit.

In Part B, safety telephone calls will be performed on BD-D15, BD-D22, and every 4 weeks from BD-D59 to BD-D149 (BD-D59, BD-D89, BD-D119, and BD-D149) to collect information about occurrence of AEs, MAAEs (including biopsy-proven organ rejection), SAEs, AESIs,

AEs leading to discontinuation from dosing and/or study participation (withdrawal), concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.5.8).

All safety laboratory assessments will be conducted at laboratories local to the study sites. To help monitor for potential event of organ transplant rejection in the SOT recipients, safety laboratory assessments will be performed, including assessments related to kidney and liver function (eg, serum creatinine, urine protein, and UPCR for kidney SOT recipients; and ALT, AST, ALP, and bilirubin for liver SOT recipients) at prespecified study visits. After Day 57 (unvaccinated SOT recipients who receive 2 vaccine doses [Group A1]) or after Day 113 (unvaccinated SOT recipients who receive 3 vaccine doses [Group A2]) or after Day 29 (previously vaccinated SOT recipients who receive dose 3 [Group A3] or SOT recipients who completed the primary vaccination series who receive BD [Group B4]), the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as applicable), and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the end of study.

A confirmed diagnosis of organ transplant rejection will be based on histologic assessment or tissue biopsy. The investigator must review results of safety laboratory assessments as soon as they are available. The schedule of sampling for safety laboratory assessments is presented in the applicable SoE.

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the applicable SoE. At dosing visits, vital sign measurements will be collected once before injection and at least 30 minutes after injection (before participants are discharged from the study site).

Physical examinations will be conducted according to the applicable SoE. A full physical examination will be performed at Day 1 and symptom-directed physical examinations will be performed at other time points.

Immunogenicity Assessments:

Blood samples for immunogenicity assessments will be collected at the time points indicated in the applicable SoE. The following analytes will be measured:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

- Serum binding antibody (bAb) against SARS-CoV-2 S protein measured by ligand binding assay specific to the SARS-CoV-2 S protein

Assessments for SARS-CoV-2 Infection

Study participants will have NP samples collected for SARS-CoV-2 testing by RT-PCR at time points specified in the applicable SoE. A study illness visit or a consultation will be arranged within 72 hours or as soon as possible to collect an NP or nasal swab sample (NP is preferred) to ascertain the presence of SARS-CoV-2 via RT-PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the US Centers for Disease Control and Prevention
- Close contact exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

If the participant had known close contact exposure to COVID-19 (eg, close contact exposure to someone with confirmed COVID-19), it will be captured in the COVID-19 exposure form.

If scheduled, the study illness visit may collect additional clinical information at the investigator's discretion, including but not limited to medical history, physical examination, blood sampling for clinical laboratory testing, and nasal, saliva, and/or NP swab sampling for viral PCR (including multiplex PCR for respiratory viruses, including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. During this visit, a blood sample will also be collected for immunologic assessment of SARS-CoV-2. All findings will be recorded in the eCRF.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant and the participant's primary care physician of the diagnosis. If the study participant does not have a primary care physician, the investigator will assist them in obtaining one. The participant will also be instructed on infection prevention measures consistent with local public health guidance.

Any confirmed symptomatic SARS-CoV-2 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

Exploratory Assessments:

Qualitative and quantitative measures of viral load of SARS-CoV-2 will be assessed by RT-PCR material from NP swab samples obtained at illness visits. Any SARS-CoV-2 genetic sequencing will be performed on the same samples.

In Part A, cellular immune response (eg, markers of CMI, T-cells, and B-cells) will be assessed on Day 1 before vaccination and at Days 36 and Day 92 in a subset of up to 50 unvaccinated participants who receive 3 doses of vaccine in the SOT group (kidney or liver) (Group A2); from 20 unvaccinated healthy study participants (Group A5) (Day 1 before vaccination and Day 36); and from a subset of at least 50 previously vaccinated SOT recipients who receive dose 3 (Group A3) (Day 1 before vaccination and Day 8). In Part B Booster Phase, CMI will also be assessed on BD-D1 before vaccination and BD-D8 from all participants in Part B. In Part B Booster Phase, blood sample will be collected for future biomarker analysis.

Statistical Methods:

Sample Size:

The planned sample size of approximately 240 participants (220 unvaccinated or previously vaccinated participants who have had a kidney or liver transplant and 20 unvaccinated healthy participants) who receive 2-dose regimen or 3-dose regimen of 100 μg of mRNA-1273, or 100 μg BD regimen are expected to provide useful estimates of Ab response at Day 29 for previously vaccinated SOT recipients who receive dose 3 in Part A, Day 113 for unvaccinated SOT recipients who receive the 3-dose regimen, at Day 57 for unvaccinated participants who receive the 2-dose regimen, and at BD-D29 (participants who receive a BD) (primary endpoints), respectively, for comparison to results from Study P301 (if available at the time of database lock). The healthy adult participants will be used primarily as a biological control for the CMI analysis. This study is designed for estimation purposes, and no between-group comparisons are planned.

Analysis Sets:

The analysis sets are defined in the following table:

Analysis Set	Description
Full Analysis Set (FAS)	All participants who received at least 1 dose of vaccine.
Modified Intent-to-Treat Set (mITT)	All participants who have negative SARS-CoV-2 status at baseline, defined as who have a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline.

Per-Protocol (PP) Subset	All participants in the mITT set who receive all planned doses of study vaccination per schedule and have no major protocol deviations that impact key or critical data.
PP Immunogenicity Subset	All participants who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise. The PP Immunogenicity Set will serve as the primary population for the analysis of SARS-CoV-2-specific bAb and nAb immunogenicity data.
Solicited Safety Set	All participant in the FAS who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All participants who received at least 1 dose of vaccine. The Safety Set will be used for all analyses of safety except for the solicited ARs.

Abbreviations: AR = adverse reaction; bAb = binding antibody; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; vaccine = investigational product.

Safety Analyses:

Given that the study does not have a concurrent unvaccinated SOT control group, descriptive statistics will be used to present safety data, and no comparisons with the healthy adult participants will be made.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be summarized by cohort and subcohort arm.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), biopsy-proven organ rejection, safety laboratory assessments, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day Follow-up Period after each dose will be summarized.

The number and percentage of participants with unsolicited AEs, SAEs, AESIs, MAAEs, Grade 3 or higher ARs and AEs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), and biopsy-proven organ rejection will be summarized. Unsolicited AEs will be presented by Medical Dictionary for Regulatory Activities preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, AESIs, MAAEs, and adjudicated biopsy-proven organ rejection will be reported in summary tables.

Clinical laboratory data will be summarized by severity for each visit and as the maximum over all postvaccination visits. Graphical presentations may include box plots and shift plots. Evaluation of clinically significant changes in safety laboratory measurements will be considered independent of the toxicity grading scale.

For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the statistical analysis plan (SAP).

Immunogenicity Analyses:

The SAP will describe the complete set of immunogenicity analyses. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. In Part A, the primary immunogenicity objective of this study is to evaluate serum Ab responses obtained 28 days after the second or third injection of 100 µg mRNA-1273 (Day 57 in unvaccinated

participants who receive 2 doses, Day 113 for unvaccinated SOT recipients who receive 3 doses, and Day 29 for previously vaccinated SOT recipients who receive dose 3). In Part B, the primary immunogenicity objective of this study is to evaluate serum Ab responses obtained 28 days after the BD. The results of the study will be described and evaluated against the Ab responses of adult healthy participants in this study and Study P301 (if available at the time of database lock).

Using the Ab threshold established from Study P301 (if available at the time of database lock), an additional exploratory analysis will be performed by measuring the proportion of participants with a serum Ab level at Day 57 (unvaccinated participants who receive 2 doses), Day 113 (unvaccinated SOT recipients who the receive 3 doses), and Day 29 (previously vaccinated SOT recipients who receive dose 3) in Part A, and at BD-D29 (participants who receive a BD) greater than or equal to the Ab threshold of protection against COVID-19, with a 2 sided 95% CI using the Clopper Pearson method by cohort arm.

The GM level of serum Ab with corresponding 95% CI will be provided at each time point by cohort 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. Additionally, the proportion of participants with a 2×, 3×, and 4× rise in GM level from Day 1 will be measured.

All nAb and bAb endpoints will be summarized at each time point with Day 29 (previously vaccinated SOT recipients who receive dose 3) and Day 57 and Day 113(unvaccinated participants), and at BD-D29 (participants who receive a BD) as the time points of interest. The GM levels and GM fold rise of both nAb and bAb will be provided with corresponding 95% CIs. Reverse cumulative distribution curves for antibody titers for all time points will be presented.

Incident Cases of COVID-19 After Vaccination:

The number and percentage of participants with COVID-19 after vaccination in the SOT recipient and healthy cohorts will be provided. The number and percentage of participants with severe COVID-19 will be provided similarly.

For serologically confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate will be provided by the healthy cohort arm.

As an additional analysis, the number and percentage of participants with symptomatic and asymptomatic COVID-19 or SARS-CoV-2 infection throughout the study will be summarized.

Study Analyses:

Interim Analyses:

An interim analysis of safety and immunogenicity data is planned after Day 57 (28 days after the second dose for unvaccinated participants), after Day 29 (28 days after dose 3 in previously vaccinated SOT recipients) in Part A, and at BD-D29 (28 days after BD in participants who receive a BD) in Part B; a clinical study report (CSR) will be prepared. An analysis of safety and/or immunogenicity may be performed at the Sponsor's discretion based on the availability of data.

Final Analysis:

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

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

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LIST OF ABBREVIATIONS AND TERMS

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

Abbreviation or Specialist Term	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
bAb	binding antibody
BD	booster dose
CDC	US Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CMI	cell-mediated immunity
cMRI	cardiac magnetic resonance imaging
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
ECG (or EKG)	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ERD	enhanced respiratory disease

EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FIO2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	geometric mean
GMT	geometric mean titer
GMFR	geometric mean fold rise
HCP	healthcare practitioner
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IM	intramuscular(ly)
IRB	institutional review board
IST	internal safety team
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mITT	modified intent-to-treat
MN	microneutralization
mRNA	messenger RNA
nAb	neutralizing antibody
NHP	nonhuman primate
NP	nasopharyngeal
PaO2	partial pressure of oxygen
PCR	polymerase chain reaction

PP	per protocol
Previously vaccinated	SOT recipients who were previously vaccinated with 2 doses of the Moderna COVID-19 vaccine under the EUA prior to enrollment
PsVNT	Pseudovirus neutralization titer (ID50)
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
S2P	SARS-CoV-2 spike protein modified with 2 proline substitutions to stabilize the spike protein in a prefusion conformation
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SM-102	heptadecane-9-yl8-((2hydroxyethyl)(6oxo6-(undecyloxy)hexyl)amino)octanoate
SoE	schedule of events
SOT	solid organ transplant
SpO2	oxygen saturation
SRC	safety review committee
Study P301	Phase 3 clinical endpoint efficacy study mRNA-1273-P301; NCT04470427
Th1	T helper cell 1
UPCR	urine protein to creatinine ratio
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Rationale

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronaviruses are zoonotic, meaning they are transmitted between animals and people. An outbreak of the CoV disease 2019 (COVID-19) caused by SARS coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 215 other countries, territories, and areas including the United States (WHO 2020a). On 11 Mar 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic. As of 26 Mar 2021, the WHO dashboard (WHO 2020b) reported there have been 2,744,543 COVID-19 deaths worldwide and more than 500,000 deaths in the United States. The US Centers for Disease Control and Prevention (CDC) have reported that the highest risk of disease burden is in older adults (≥ 65 years old) and in people of any age who have serious underlying medical conditions, such as chronic lung disease or moderate to severe asthma, serious heart conditions, severe obesity, diabetes, chronic kidney disease requiring dialysis, and liver disease, and in those who are immunocompromised (CDC 2020a).

Immunocompromised populations, such as individuals who are solid organ transplant (SOT) recipients, are at especially high risk for increased complications of COVID-19 because of their associated co-morbidities and chronic immunosuppression. A recent meta-analysis of 215 studies assessing clinical outcomes of COVID-19 in SOT recipients (kidney, liver, heart, and lung) internationally showed an overall mortality rate of 18.6% (Raja et al 2020). Initial results on the clinical outcomes of COVID-19 estimated a high mortality rate ranging between 13% and 39% in kidney transplant recipients (Azzi et al 2020 [patients in the US]; Cravedi et al 2020 [patients in the US, Italy, and Spain]; Lubetzky et al 2020 [patients in the US]; Mehta et al 2020 [patients in the US]; Nair et al 2020 [patients in the US]; Pereira et al 2020 [patients in the US]) and 12% in European liver transplant recipients (Bechetti et al 2020). In a recent prospective cohort study, (Walsh et al 2020) a low proportion (17%) of SOT recipients mounted a positive antibody response to the first dose of SARS-CoV-2 messenger RNA (mRNA) vaccines, with those who receive anti-metabolite maintenance immunosuppression less likely to respond (Boyarsky et al 2021a). In the published follow-up study (Boyarsky et al 2021b), antibody response was assessed after the second dose. Overall, of the 658 participants, 98 (15%) had measurable antibody response after dose 1 and dose 2; 301 (46%) had no antibody response after dose 1 or dose 2; and 259 (39%) had no antibody response after dose 1 but had subsequent antibody response after dose 2. In addition, recent data based on post-Emergency Use Authorization (EUA) experience show that SOT recipients' immune response to mRNA-based vaccination has been shown to be substantially lower than what has been reported in the general population with antibody responses detectable in

only 30-60% after 2 doses (Benotmane et al 2021; Boyarsky et al 2021b, Grupper et al 2021; Marinaki et al 2021).

A more recent small case series evaluated the antibody responses and vaccine reactions in 30 SOT recipients who had suboptimal response to standard vaccination (Moderna or Pfizer COVID-19 vaccine) and subsequently received a third dose of the vaccine (either Janssen, Moderna, or Pfizer COVID-19 vaccine), the investigators observed that of the 6 patients with low-positive antibody titers before the third dose, all had high-positive antibody titers after the third dose. In contrast, of the 24 patients with negative antibody titers before the third dose, only 6 (25%) had high-positive antibody titers after the third dose. Two (8%) had low-positive antibody titers, and 16 (67%) remained negative (Werbel et al 2021).

In addition, a recently published article described a double-blind, randomized, controlled trial of a third dose of mRNA-1273 vaccine (Moderna) as compared with placebo (NCT04885907; Hall et al 2021). The results demonstrated that a third dose of mRNA-1273 vaccine in transplant recipients elicited a substantially higher immune response than placebo, as determined in the analysis of both primary and secondary trial endpoints. The third dose was considered safe when risk versus benefit was considered.

Interim data are available from an ongoing Moderna Phase 2 study, mRNA-1273-P201 (Study P201) where healthy adult participants in Study mRNA-1273-P201 received 2 doses of either 50 µg or 100 µg of mRNA-1273 and were administered a 50 µg booster of mRNA-1273 6 to 8 months after the second dose. Participants in mRNA-1273-P201 who received the booster dose (BD), demonstrated enhanced immune responses to SARS-CoV-2 compared to pre-boost levels and met the noninferiority criteria stipulated in the US Food and Drug Administration Guidance on EUA for Vaccines to Prevent COVID-19. Available data also show that heterologous or mixed series of COVID-19 vaccine induced high immune response in the adult population (Atmar et al 2021). Additionally, no new safety signals emerged upon administration of the BD in Study P201. Based on cumulative evidence, the benefit-risk profile of a BD of mRNA-1273 is favorable, particularly in light of increasing breakthrough disease with the emergence of the Delta variant. Providing the option for a BD to all eligible participants currently enrolled in the study as well as enrolling eligible SOT recipients who completed primary vaccination series under EUA is expected to generate valuable homologous and heterologous booster data in the immunocompromised population.

The study vaccine, mRNA-1273, is currently being evaluated in a pivotal Phase 3 efficacy, safety, and immunogenicity study in an adult population at high risk of COVID-19 disease (Study P301). Success criteria for early efficacy were met at first interim analysis based on 95 adjudicated cases with a vaccine efficacy of 94.5% (95% CI: 86.5%, 97.8%; one-sided p-value < 0.0001). However, immunocompromised individuals were excluded from this study. The current study aims to

evaluate the antibody (Ab) responses following the second or third dose of mRNA-1273 vaccine among adult recipients of kidney or liver transplants. The data are expected to provide clinical information whether this population of immunocompromised participants are able to mount an antibody response following vaccination compared with adult participants with normal immune function.

1.2. Background and Overview

The Sponsor has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then display 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. Messenger RNA vaccines have been used to induce immune responses against infectious pathogens such as SARS-CoV-2 (NCT04283461, NCT04405076), cytomegalovirus (NCT03382405), metapneumovirus and parainfluenza virus type 3 (NCT03392389), Zika virus (NCT04917861), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP) encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 encodes the full-length spike (S) protein of SARS-CoV-2, modified with 2 proline substitutions to stabilize the S protein in a prefusion conformation (S2P). 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 (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020). It has been confirmed that the stabilized SARS-CoV-2 S2P expresses well and is in the prefusion conformation (Wrapp et al 2020). More details on mRNA-1273 and its variants are provided in the Investigator's Brochure (IB).

The development of the mRNA-1273 vaccine is being accelerated to address the current SARS-CoV-2 outbreak as a result of the uniquely rapid and scalable manufacturing process for the mRNA-1273 vaccine.

1.2.1. Nonclinical Studies

Nonclinical pharmacology, biodistribution, and toxicology studies have been completed using mRNA-1273 or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs. Data from the nonclinical testing program support the clinical efficacy and safety of mRNA-1273 at doses up to 100 µg administered twice, intramuscularly (IM), 28 days apart.

- mRNA-1273 induced high levels of binding and neutralizing antibodies in young and aged mice, rats, hamsters, and nonhuman primates (NHPs); protected against viral replication in the upper (nasal turbinates) and lower (lung) airways; and did not promote vaccine-associated enhanced respiratory disease (ERD) in these nonclinical models.
- The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of IM drug products and distribution via the lymphatic system. mRNA does not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and spleen, in which the average half-life values ranged from 14.9 to 63.0 hours.
- The rat aggregate Good Laboratory Practice (GLP) repeat-dose toxicity data of mRNA vaccines developed with the Sponsor's mRNA-based platform, together with results from the mRNA-1273 non-GLP study, demonstrate a similar, consistent, and acceptable toxicity profile supportive of the clinical development of mRNA-1273.
- Results from the GLP developmental and reproductive toxicity study showed that administration of a 100 µg dose of mRNA-1273 to Sprague Dawley rats did not result in any adverse effects on dams, fetuses, or pups and demonstrated a strong transfer of SARS-CoV-2 S2P antibodies from dam to fetus and from dam to pup. Results from this study support the safety of mRNA-1273 for trials in pregnant women.

In support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the IB along with nonclinical experience with modified mRNA-1273 vaccines.

1.2.2. Clinical Studies

The clinical development of mRNA-1273 vaccines to support its use in the adult population consists of 5 ongoing clinical trials being conducted in the US:

- Phase 1, open-label, dose ranging studies (Study 20-0003; NCT04283461; Study 21-0002, NCT04785144) sponsored by the National Institute of Allergy and Infectious Diseases
- Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study (Study mRNA-1273-P201; NCT04405076)

- Phase 3 randomized, stratified, observer-blind, placebo-controlled study (Study mRNA-1273-P301; NCT04470427) to evaluate the efficacy, safety, and immunogenicity of the vaccine
- Phase 3b, open-label study (Study mRNA-1273-P304, NCT04860297) to evaluate the safety and immunogenicity of the vaccine in adult SOT recipients and healthy controls.

In addition, 2 ongoing trials are being conducted in the pediatric population:

- Phase 2/3 randomized, placebo-controlled safety and immunogenicity study of mRNA-1273 in children 12 to less than 18 years of age (Study mRNA-1273-P203; NCT04649151)
- Phase 2/3, study to evaluate the safety and immunogenicity of mRNA-1273 in children less than 12 years of age (mRNA-1273-P204; NCT04796896).

In addition, Study mRNA-1273-P205 (NCT04927065) is an open-label, Phase 2/3 study with multiple parts to evaluate the safety and immunogenicity of boosters for SARS-CoV-2 variants.

The safety and immunogenicity of mRNA-1273 was evaluated in Phase 1 (Division of Microbiology and Infectious Diseases [DMID] 20-0003) and Phase 2 (mRNA-1273-P201) studies, which were important in selecting and confirming the dose of the vaccine used in the pivotal Phase 3 study.

In Study 20-0003 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of nAb or binding antibody (bAb) with an acceptable safety profile, and this observation was the basis for selecting the 100-µg dose for use in the pivotal Phase 3 study. Importantly, the Ab levels after 2 doses of mRNA-1273 exceeded those from a pool of convalescent sera. Neutralizing activity was observed for the 100 µg mRNA-1273 dose as of Day 36 and was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. In this study, the majority of the solicited adverse reactions (ARs) were mild or moderate. A higher incidence of severe solicited ARs was observed with the 250 µ dose (in the 18 to 55-year age cohort) compared with the lower doses (25 µg, 50 µg, and 100 µg); thus, the 250-µg mRNA-1273 dose was not evaluated in participants ≥ 56 years of age. One severe unsolicited adverse event (AE) related to mRNA-1273 and 1 severe clinically meaningful elevation in serum lipase related to mRNA-1273 were also observed with the 250 µg dose (in the 18 to 55-year age cohort). Additionally, in Study 20-0003, T helper cell 1 (Th1) directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response, and similar responses were observed among all age groups for the 100-µg dose. The predominance of a Th1 directed T-cell profile helps to mitigate concern of the risk of enhanced disease associated with Th2 driven pathophysiology.

mRNA-1273-P201 (Study P201) is an ongoing Phase 2a, safety, reactogenicity, and immunogenicity study in healthy adults that provided confirmation of the immunogenicity of both

the 100 µg and 50 µg doses. The study was designed as a randomized, observer-blind, placebo-controlled dose-confirmation study (Part A). Two mRNA-1273 dose levels, 50 µg and 100 µg, and placebo were evaluated in 2 age cohorts: Cohort 1 enrolled participants ≥ 18 to < 55 years old (300 participants), and Cohort 2 enrolled participants ≥ 55 years old (300 participants). A total of 600 participants received either mRNA-1273 or placebo according to a 1:1:1 randomization ratio, ie, within each age cohort, 100 participants each received mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo.

An amendment to the Study 201 protocol adapted the study design to include open-label interventional phases (Part B and Part C). Part B allowed unblinding of participants and offered 2 injections of mRNA-1273 in an open-label manner, 28 days apart, to all participants who received placebo in Part A. Part B also offered a single BD of mRNA-1273 (50 µg) to participants who received 1 or 2 doses of mRNA-1273 (50 µg or 100 µg) in Part A. Part C was prompted by the need to proactively prepare for vaccination strategies that might induce broader protection, including against emerging variants of SARS-CoV-2 such as B.1.351. Part C enrolled participants from Study 301 who received 2 doses of mRNA-1273 100 µg at least 6 months prior. Part C participants received a single injection of mRNA-1273.351 (20 µg or 50 µg) or mRNA-1273.351 mixture (50 µg total – 25 µg of mRNA-1273 and 25 µg of mRNA-1273.351). mRNA-1273 demonstrated an acceptable safety profile in the participant population enrolled in this study at both dose levels and both age cohorts, as observed through 6 months after the second injection. Vaccination with mRNA-1273 in Study 201 resulted in robust immune responses to SARS-CoV-2 in participants 18 years and older at both dose levels, and persistence of immune response was observed up to 6 months after the second injection in Part A of the study. In Part A of Study 201, the time course and magnitude of antibody (both bAb and nAb) responses to mRNA-1273 was similar between 100 µg and 50 µg dose levels at each postbaseline time point (Days 29, 43, 57, and 209), although the 100 µg dose group had numerically greater responses (and was the dose selected for the pivotal Phase 3 efficacy study). In Part B of Study 201, administration of a 50 µg BD of mRNA-1273 6 months or more after the primary series improved the immune responses to 1.7-fold the peak achieved after the primary vaccination series in the current mRNA-1273-P301 study, where efficacy of mRNA-1273 against COVID-19 was demonstrated. Safety data based on preliminary results for 50 µg BDs of mRNA-1273 (selected participants in Part B) or mRNA-1273.351 (Part C Cohort 1) are available. Percentages of participants with solicited local and systemic AEs were similar in the group who received mRNA-1273.351 as a BD compared to those who received mRNA-1273 vaccine as a BD. The majority of solicited local and systemic AEs were mild (Grade 1) or moderate (Grade 2). The frequency of any Grade 3 solicited local or systemic AE was 15% (3 of 20 participants) after the BD of mRNA-1273 and 10.5% (2 of 19 participants) after the BD of mRNA-1273.351. There were no Grade 4 solicited local or systemic AEs. The most common solicited local AE was injection site pain after injection in both groups

(68.4% for the mRNA-1273.351 vaccine and 90.0% for the mRNA-1273 vaccine). The most common solicited systemic AEs after the BD of the mRNA-1273.351 vaccine were fatigue (36.8%), headache (36.8%), myalgia (31.6%), and arthralgia (21.1%). The most common solicited systemic AEs after the BD of the mRNA-1273 vaccine were fatigue (70.0%), headache (55.0%), arthralgia (50.0%), and myalgia (45.0%). Fever was reported after the BD of mRNA-1273 in 3 of 20 participants (15%) but not after the booster dose of mRNA-1273.351 (0 of 19 participants). There were no SAEs reported in this study.

Interim results from the mRNA-1273-P205 study are available. Neutralizing antibodies against Omicron were assessed in a pseudovirus neutralization titer (ID50) (PsVNT) assay conducted at laboratories established by the National Institute of Allergy and Infectious Diseases' Vaccine Research Center and Duke University Medical Center - Data includes sera from 20 booster recipients each of mRNA-1273 at the 50 µg and 100 µg dose levels, multivalent candidate mRNA-1273.211 at the 50 µg and 100 µg dose levels, and multivalent candidate mRNA-1273.213 at the 100 µg dose level.

All groups had low neutralizing antibody levels in the Omicron PsVNT assay prior to boosting. At Day 29 post boost, the authorized 50 µg booster of mRNA-1273 increased neutralizing geometric mean titers (GMT) against Omicron to 850, which is approximately 37-fold higher than pre-boost levels. At Day 29 post boost, the 100 µg dose booster of mRNA-1273 increased neutralizing GMT to 2228, which is approximately 83-fold higher than pre-boost levels. The multivalent candidates boosted Omicron specific neutralizing antibody levels to similarly high levels at both the 50 µg and 100 µg levels.

Safety and tolerability data from the Phase 2/3 study of the 100 µg booster dose of mRNA-1273 (N = 305) show that a 100 µg booster dose of mRNA-1273 was generally safe and well tolerated. The frequency and nature of solicited systemic and local AEs 7 days after receiving a booster were generally comparable to those seen after the 2-dose primary series. There was a trend toward more frequent local and systemic solicited ARs following the 100 µg booster dose relative to the authorized 50 µg booster dose of mRNA-1273.

Currently, a Phase 3 pivotal, randomized, placebo-controlled, observer-blind clinical study (mRNA-1273-P301; NCT04470427; Study P301) is being conducted in participants 18 years of age and older who were at increased risk of COVID-19 disease. In addition, prespecified cohorts of participants who were either ≥ 65 years of age or 18 to < 65 years of age with comorbid medical conditions were included. At the time of the 25 Nov 2020 data snapshot (which was the basis for the EUA), a total of 30,351 participants were followed for a median of 92 days (range: 1-122 days) for the development of COVID-19 disease (Moderna mRNA-1273 IB). Success criteria for early efficacy were met at the first interim analysis based on 95 adjudicated cases with a vaccine efficacy

of 94.5% (95% CI: 86.5%, 97.8%; one-sided p value < 0.0001). Study P301 is expected to provide immunogenicity data where an Ab threshold of protection against COVID-19 will be estimated.

In Study P301, solicited ARs were reported more frequently among vaccine participants than placebo participants. The most frequently reported ARs after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70% any grade; 10.1% grade ≥ 3), headache (64.7% any grade; 5.7% grade ≥ 3), myalgia (61.5% any grade; 9.1% grade ≥ 3), and chills (45.4% any grade; 1.4% grade ≥ 3). 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. In the participants who received the vaccine, solicited systemic ARs were reported numerically more frequently by vaccine participants after dose 2 than after dose 1. Grade 3 systemic ARs (fatigue, myalgia, arthralgia, and headache) were reported more frequently after dose 2 than after dose 1.

Unsolicited AEs and serious adverse events (SAEs) were reported at generally similar rates in participants who received mRNA-1273 and placebo from the first dose until the last observation. 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% of versus 0.6%). All of the lymphadenopathy events are similar to the axillary swelling/tenderness in the injected arm reported as solicited ARs. 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. Delayed injection site reactions that began >7 days after vaccination were reported in 1.2% of vaccine recipients and 0.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

There were 3 reports of Bell's palsy in the mRNA-1273 vaccine group (one of which was an SAE), which occurred 22, 28, and 32 days after vaccination, and one in the placebo group, which occurred 17 days after vaccination. The currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. 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 treatment groups for specific categories of AEs (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

Efficacy and safety results based on the final analysis of Part A with a database lock of 04 May 2021 are provided in the IB. The results are generally comparable to the interim analysis. On 25 Aug 2021, Moderna announced that it had completed the rolling submission process for its Biologics License Application to the Food and Drug Administration (FDA) for the full licensure of the Moderna COVID-19 vaccine (mRNA-1273) for active immunization to prevent COVID-19 in individuals 18 years of age and older. mRNA-1273 has been showing durable efficacy of 93% through 6 months after the second dose.

In the post-EUA period, anaphylaxis has been reported following mRNA-1273 administration. There have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines; however, no cases of myocarditis were observed in the clinical program.

A detailed review of the clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits from Participation

The following benefits may accrue to participants:

- The mRNA-1273 vaccine may be effective to prevent COVID-19.
- 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 for immunocompromised individuals.

1.3.2. Risks to Study Participants and Risk Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. The risk of anaphylaxis after all vaccines is estimated to be 1.31 (95% CI, 0.90-1.84) per million vaccine doses (McNeil and DeStefano 2018). Anaphylaxis has been reported in the post-EUA period for mRNA-1273 (more than 7.7 million doses administered; CDC 2021a), although not in the ongoing Study P301, at the time of the 25 Nov 2020 data snapshot (Section 1.2.2). In the post-EUA period, the rate of anaphylaxis following first dose of Moderna COVID-19 vaccine from 21 Dec 2020 to 10 Jan 2021 was estimated to be 2.5 cases per million doses administered, and most cases occurred in individuals with a history of allergic reactions or anaphylaxis unrelated to

vaccines (CDC 2021b). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

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

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection.

A summary of the safety profile of the mRNA-1273 vaccine observed during the ongoing Stud P301 is presented in Section 1.2.2.

There is a theoretical risk that active vaccination to prevent SARS-CoV-2 infection may cause a paradoxical increase in the risk of COVID-19. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles virus (Fulginiti et al 1967). Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2019).

In order to address this theoretical risk, animal studies were performed in young and aged wild type mice and rhesus macaques (NHPs). These studies were designed to capture immunogenicity endpoints that would be predictive of ERD and also to evaluate if, at protective or subprotective dose levels of mRNA-1273, evidence of disease enhancement would be observed after challenge of the animals with SARS-CoV-2. These nonclinical studies demonstrated that mRNA-1273 is safe and well tolerated in different animal species; is immunogenic; drives a robust SARS-CoV-2 specific Ab, neutralization, and Th1 directed CD4+ T-cell response; fully protects animals from challenge at dose levels as low as 1 µg/dose in mice and 30 µg/dose in NHPs; and does not lead to ERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from the DMID Phase 1 study of mRNA-1273 demonstrated high levels of nAbs and Th1 polarized CD4+ T-cell responses (Jackson et al 2020), consistent with the immunogenicity observed in these nonclinical studies. Lastly, in Study P301, after a median follow-up of 2 months after the second dose of vaccine, the overwhelming majority of COVID-19 cases occurred in participants who received placebo rather than mRNA-1273 (Baden et al 2020), consistent with a low risk of ERD following vaccination with mRNA-1273. These data suggest that a paradoxical increase in the risk of disease, while not eliminated, is likely to be low.

In the context of the EUA for individuals 18 years and older for mRNA-1273, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 vaccine. Although causality has not been established, the majority of the cases have been reported in young males within 7 days 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 (Gargano et al 2021).

The AEs after receiving a third dose of mRNA-1273 are described in Section 1.2.2. In general, solicited local and systemic adverse reactions after the BD (Study P201) were comparable to what had been observed with the primary series (Study P301). The AEs after receiving a 100 µg booster dose of mRNA-1273 are described in Section 1.2.2. The frequency and nature of solicited systemic and local AEs 7 days after receiving a 100 µg booster dose of mRNA-1273 were generally comparable to those seen after the 2-dose primary series. There was a trend toward more frequent local and systemic solicited ARs following the 100 µg booster dose relative to the authorized 50 µg booster dose of mRNA-1273. The AEs after receiving a fourth dose are currently being evaluated. It is unknown if the AEs after getting a fourth dose of mRNA-1273 are different from getting 2 or 3 doses of mRNA-1273.

1.3.3. Overall Benefit/Risk Conclusion

In Part A, all healthy participants (Group A5) will benefit from the 2-dose regimen of 100 µg mRNA-1273 vaccine administered in 2 doses 28 days apart, the same regimen and dose that received EUA. All SOT unvaccinated recipients will receive the same 2-dose regimen (Group A1) and also be offered the option of receiving a third dose on Day 85 (Group A2) (Section 3.1). All previously vaccinated SOT recipients who received 2 doses of the Moderna COVID-19 vaccine outside of the study will receive a third dose on Day 1 (Group A3). In the booster phase Part B, all participants in Part A will be offered to receive a 100 µg BD of mRNA-1273 (Group B2, Group B3, and Group B5); Eligible SOT recipients who completed primary vaccination series under EUA will be enrolled and given a 100 µg BD of mRNA-1273 (Group B4).

Safety will be monitored throughout the study (Section 7.6).

Considering the limited number of approved vaccines for COVID-19, the participants' risk of COVID-19 outside the study during a pandemic, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

2. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Part A	
Primary Objectives	**Primary Endpoints**
• To evaluate the safety of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens	• Unsolicited adverse events (AEs) through 28 days after each injection • Medically attended adverse events (MAAEs) from Day 1 and throughout the study period • Serious adverse events (SAEs) from Day 1 and throughout the study period • Adverse events of special interest (AESIs) from Day 1 and throughout the study period • AEs leading to discontinuation from dosing and/or study participation (withdrawal) on Day 1 and throughout the study period • Biopsy-proven organ rejection from Day 1 and throughout the study period
• To evaluate the reactogenicity of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimen	• Solicited local and systemic adverse reactions (ARs) through 7 days after each injection (for unvaccinated participants who received 2 doses of mRNA-1273) • Solicited local and systemic ARs through 7 days after each injection (for unvaccinated SOT recipients who received 3 doses and SOT recipients previously vaccinated outside the study who received a third dose)
• To evaluate serum neutralizing antibody (nAb) responses to doses of 100 µg mRNA-1273 obtained	• The geometric mean titer (GMT) value of serum Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)-specific nAb

Objectives	Endpoints
28 days after the second dose or third dose	level after the second dose (Day 57 for unvaccinated participants []) • The GMT value of SARS-CoV-2-specific nAb level 28 days after dose 3 (Day 113 for unvaccinated SOT recipients and Day 29 for previously vaccinated SOT recipients)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to 2 or 3 doses of 100 µg mRNA-1273, as assessed by the level of anti-SARS-CoV-2 Spike (S) specific binding antibody (bAb) through 1 year after dose 2 or dose 3	• For all unvaccinated participants, the geometric mean (GM) value of anti-SARS-CoV-2 S-specific bAb on Day 1, Day 29 (28 days after dose 1), and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GM will be evaluated on Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) o For participants receiving the 3-dose regimen, GM will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GM will be evaluated on Day 1 (dose 3), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3) • For all unvaccinated participants, the geometric mean fold rise (GMFR) of bAb relative to Day 1 on Day 29 (28 days after dose 1), and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GMFR will evaluated on Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMFR will be evaluated on Day 85 (dose 3), Day 113 (28 days after

Objectives	Endpoints
	dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GMFR of bAb relative to Day 1 (dose 3) will be evaluated on Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3)
• To evaluate the persistence of the immune response to 2 or 3 doses of 100 µg mRNA-1273, as assessed by the level of nAb through 1 year after dose 2 or dose 3	• For all unvaccinated participants, the GMT values of SARS-CoV-2-specific nAb on Day 1 and Day 29 (28 days after dose 1) o For participants in the 2-dose regimen, GMT will be evaluated on Day 209 (6 months after dose 2) and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMT will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GMT values of SARS-CoV-2-specific nAb will be evaluated on Day 1 (dose 3), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3) • For all unvaccinated participants, GMFR of nAb relative to Day 1 will be evaluated on Day 29 (28 days after dose 1) and Day 57 (28 days after dose 2) o For participants receiving the 2-dose regimen, GMFR will be evaluated on Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) o For participants in the 3-dose regimen, GMFR will be evaluated on Day 85 (dose 3), Day 113 (28 days after dose

Objectives	Endpoints
	3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) • For all previously vaccinated SOT recipients, GMFR of nAb relative to Day 1 (dose 3) will be evaluated on Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (1 year after dose 3)
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult solid organ transplant (SOT) recipients and healthy adult participants with negative SARS-CoV-2 at baseline	• The incidence of asymptomatic SARS-CoV-2 infection among recipients of mRNA-1273 SARS-CoV-2 vaccine will be defined in participants with negative SARS-CoV-2 at baseline as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that become positive (as measured by Roche Elecsys) counted starting 28 days after the second dose and 28 days after the third dose of vaccine, OR • Positive reverse transcriptase polymerase chain reaction (RT-PCR) counted starting 14 days after the second and after the third dose of vaccine
• To describe the incidence of coronavirus disease 2019 (COVID-19) after vaccination with mRNA-1273 in SOT recipients and healthy participants	• First occurrence of COVID-19 starting 14 days after the second dose and after the third dose of vaccine, where COVID-19 is defined as symptomatic disease based on the following criteria • The participant must have experienced at least TWO of the following symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, or new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or

Objectives	Endpoints
	radiographical evidence of pneumonia, AND • The participant must have at least 1 nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR • First occurrence of severe COVID-19 starting 14 days after the second dose and after the third dose of vaccine, where severe COVID-19 is defined as symptomatic COVID-19 AND any of the following: o Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen saturation (SpO2) ≤ 93% on room air at sea level, or partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) < 300 mm Hg, OR o Respiratory failure or acute respiratory distress syndrome (ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation) or evidence of shock (systolic blood pressure [BP] < 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR o Significant acute renal, hepatic, or neurologic dysfunction, OR o Admission to an intensive care unit or death o The secondary case definition of COVID-19 is defined as the following symptoms: fever (temperature ≥ 38ºC) or chills, cough, shortness of breath or

Objectives	Endpoints
	difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
• To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine	• Safety laboratory assessments of kidney (serum creatinine, urine protein, and urine protein to creatinine ratio [UPCR]) and liver (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) function: o For unvaccinated SOT recipients, from Day 1 through Day 57 for SOT recipients who receive 2 doses and through Day 113 for SOT recipients who receive 3 doses of mRNA-1273 o For previously vaccinated SOT recipients, from Day 1 (dose 3) through Day 29 (28 days after dose 3)
• To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine	• Change in immunosuppressant medications to treat organ transplant rejection or to improve immune tolerance from Day 1 and throughout the study period. Change in immunosuppressant medication is defined as any of the following: o any adjustments (temporarily or permanently) in immunosuppressants, o addition of new immunosuppressants, o or switching from 1 maintenance rejection prophylaxis regimen to another.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of	• Comparison of genetic sequence of viral isolates with that of the vaccine sequence

Objectives	Endpoints
isolated SARS-CoV-2 strains to the vaccine sequence	
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative immunoglobulin G [IgG]) and percent of study participants with 2×, 3×, and 4× rise of bAb relative to baseline
• To assess, in a subset of SOT recipients who received 3-dose regimen and healthy participants who received 2-dose regimen, SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T-cells as measured by flow cytometry at Day 1, Day 36, and Day 92 for unvaccinated SOT recipients, at Day 1 and Day 8 for previously vaccinated SOT recipients, and at Day 1 and Day 36 in healthy participants
• To define, in a subset of SOT recipients who received 3-dose regimen and healthy participants, the epitopes recognized by B-cells and antibodies generated in response to mRNA-1273	• Magnitude and phenotype of S protein-specific B-cells as measured by flow cytometry at Day 1, Day 36, and Day 92 for unvaccinated SOT recipients, at Day 1 and Day 8 for previously vaccinated SOT recipients, and at Day 1 and Day 36 in healthy participants • Determination of targeted major antigenic sites and amino acid residues on SARS-CoV-2 S protein

Objectives	Endpoints
Part B – Booster Phase	
Primary Objectives	**Primary Endpoints**
• To evaluate the safety of the 100 µg BD of mRNA-1273	• Solicited local and systemic ARs through 7 days after BD injection • Unsolicited AEs through 28 days after BD injection • MAAEs throughout the study period • SAEs throughout the study period • AESIs, including myocarditis/pericarditis throughout the study period • AEs leading to discontinuation from dosing and/or study participation (withdrawal) throughout the study period • • Biopsy-proven organ rejection throughout the study period
• To evaluate serum nAb responses elicited by the 100 µg mRNA-1273 obtained 28 days after the BD	• The GMT value of serum SARS-CoV-2-specific nAb level 28 days after the BD in SOT participants who received the Moderna primary series • The GMT value of SARS-CoV_2-specific nAb level 28 days after BD in SOT participants who received non-Moderna primary series
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the persistence of the immune response of the BD of mRNA 1273 vaccine (100 µg) as assessed by the level of SARS-CoV-2 S2P specific bAb through 6 months after BD	• The GM value of SARS-CoV-2 S2P specific bAb on BD-Day 1, BD-Day 29 (28 days after BD), BD-Day 181 (6 months after BD)

Objectives	Endpoints
• To evaluate the persistence of the immune response of the BD of mRNA 1273 vaccine (100 µg) as assessed by the level of nAb through 6 months after BD	• The GM values of SARS-CoV-2-specific nAb on BD-Day 1, BD-Day 29 (28 days after BD), BD-Day 181 (6 months after BD)
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with negative SARS-CoV-2 at baseline	• The incidence of asymptomatic SARS-CoV- 2 infection among recipients of mRNA-1273 SARS-CoV-2 vaccine will be defined in participants with negative SARS-CoV-2 at baseline as: o bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1, that becomes positive (as measured by Roche Elecsys) counted starting 28 days after the BD, OR o Positive RT-PCR counted starting 14 days after the BD
• To describe the incidence of COVID-19 after vaccination with mRNA-1273 in SOT recipients and healthy participants	• First occurrence of COVID-19 starting 14 days after BD of vaccine, where COVID-19 is defined as symptomatic disease based on the following criteria • The participant must have experienced at least TWO of the following symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, or new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia, AND • The participant must have at least 1 nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if

Objectives	Endpoints
	hospitalized) positive for SARS-CoV-2 by RT-PCR • First occurrence of severe COVID-19 starting 14 days after the BD of vaccine, where severe COVID-19 is defined as symptomatic COVID-19 AND any of the following: o Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen saturation (SpO2) ≤ 93% on room air at sea level, or partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) < 300 mm Hg, OR o Respiratory failure or acute respiratory distress syndrome (ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation) or evidence of shock (systolic blood pressure [BP] < 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR o Significant acute renal, hepatic, or neurologic dysfunction, OR o Admission to an intensive care unit or death. • The secondary case definition of COVID-19 is defined as the following symptoms: fever (temperature ≥ 38ºC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting or diarrhea AND a positive NP swab, nasal swab, or saliva

Objectives	Endpoints
	sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
• To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine	• Safety laboratory assessments of kidney (serum creatinine, urine protein, and UPCR) and liver (ALT, aspartate AST, ALP, and bilirubin) function from BD-D1 through BD-D29 (28 days after BD)
• To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine	• Change in immunosuppressant medications to treat organ transplant rejection or to improve immune tolerance from BD-D1 and throughout the study period. Change in immunosuppressant medication is defined as any of the following: o any adjustments (temporarily or permanently) in immunosuppressants, o addition of new immunosuppressants, o or switching from 1 maintenance rejection prophylaxis regimen to another.
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of genetic sequence of viral isolates with that of the vaccine sequence
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19

Objectives	Endpoints
• To describe the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and percent of study participants with 2×, 3×, and 4× rise of bAb relative to baseline
• To assess, in a subset of SOT recipients and healthy participants who received BD, SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T-cells BD-D1 and BD-D8
• To define, in a subset of SOT recipients and healthy participants, the epitopes recognized by B-cells and antibodies generated in response to mRNA-1273	• Magnitude and phenotype of S protein-specific B-cells as measured by flow cytometry at BD-D1 and BD-D8 • Determination of targeted major antigenic sites and amino acid residues on SARS-CoV-2 S protein

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = adverse reaction; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; bAb = binding antibody; BD = booster dose; BP = blood pressure; COVID-19 = coronavirus disease 2019; D = day; FIO2 = fraction of inspired oxygen; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = Nasopharyngeal; PaO2 = partial pressure of oxygen; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = SARS-CoV-2 spike protein modified with 2 proline substitutions to stabilize the spike protein in a prefusion conformation; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SOT = solid organ transplant; SpO2 = oxygen saturation; UPCR = urine protein to creatinine ratio.

3. STUDY DESIGN

3.1. General Design

This is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in SOT recipients and healthy controls. Adult kidney and liver transplant recipients and healthy control participants who are at least 18 years of age will be enrolled.

Approximately 240 adult participants (220 previously vaccinated or unvaccinated participants who have had a kidney or liver transplant and 20 unvaccinated healthy adults) will be enrolled. At least 50 SOT recipients who completed primary vaccination series with a non-Moderna COVID-19 vaccine under EUA (outside of the mRNA-1273-P304 study) will be enrolled in Part B (Group B4).

In Part A, all SOT recipients who were unvaccinated prior to enrollment will receive 2 doses of 100 µg of mRNA-1273 (vaccine) 28 days apart (window of -3/+7 days for the second dose) (Group A1). The SOT recipients will be offered the opportunity to receive a third primary dose of vaccine at Day 85 (window of -3/+7 days for the third dose) as per the EUA Fact Sheet available at the time of protocol finalization (Group A2). All healthy participants will receive 2 doses of vaccine 28 days apart (window of -3/+7 days for the second dose) (Group A5). SOT recipients who were previously vaccinated with 2 doses of Moderna COVID-19 vaccine under the EUA prior to enrollment will receive dose 3 on Day 1 (Group A3). These participants will be referred to as previously vaccinated throughout this document. Under Amendment #4, unvaccinated SOT participants who will be enrolled will be given 3 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose. Under Amendment #4, SOT participants previously vaccinated with 2 doses of Moderna COVID-19 vaccine outside of the study who will be enrolled will receive a third 100 µg dose in Part A then proceed to Part B to receive a 100 µg BD.

In Part B, all eligible active participants in Part A will be offered to receive a 100 µg BD of mRNA-1273 who are at least 4 months from the last dose. SOT recipients who completed primary COVID-19 vaccination series under EUA will receive a 100 µg BD on BD-D1.

The schematic of study arms and major study events is illustrated in Figure 1, Figure 2, Figure 3, and Figure 4. The schedules of events (SoEs) for the study are presented in Section 10.1. Study arms and doses are presented in Table 2.

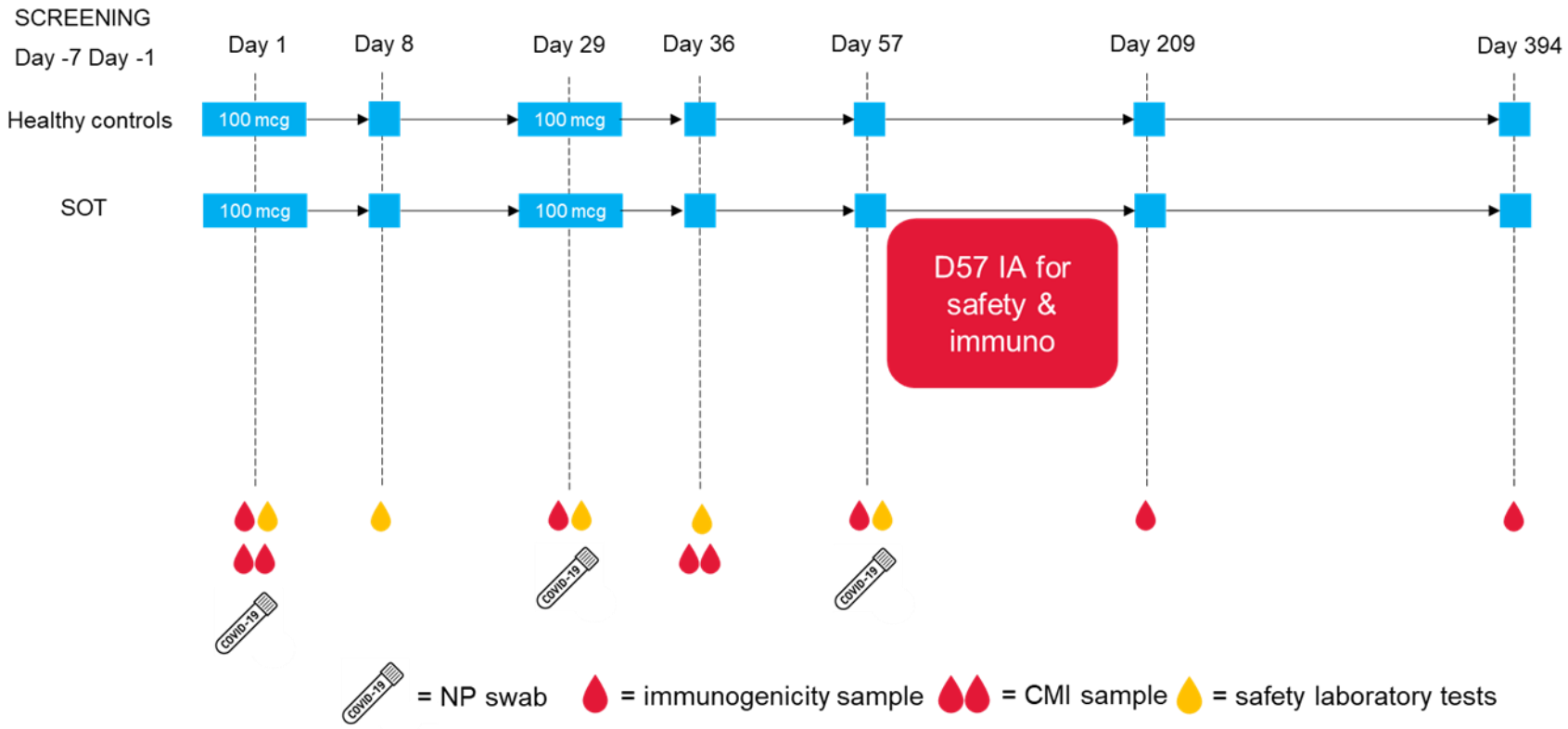
Table 2: Study Arms

Study Arm	Part A	Doses in P304 Part A	Part A Dose	Move on to Part B?	Part B	Doses in P304 Part B	Part B B-Dose	Total Doses in P304
SOT Recipient Cohorts								
Unvaccinated participants who consent to receive only 2 doses in Part A (Days 1 and 29)	**Group A1**	2	100 µg		NA	N/A	N/A	2
Unvaccinated participants who consent to receive 3 doses in Part A (Days 1, 29, and 85)	**Group A2**	3	100 µg	⇨	**Group B2**	1	100 µg	4
Participants previously vaccinated with 2 doses of the Moderna COVID-19 vaccine under the EUA who consent to receive a third dose in Part A (Day 1)	**Group A3**	1	100 µg	⇨	**Group B3**	1	100 µg	2
SOT recipients who completed primary vaccination with an mRNA or non-mRNA COVID-19 vaccine outside mRNA-1273-P304 who consent to receive 1 booster dose (in Part B)	N/A	N/A	N/A		**Group B4**	1	100 µg	1

Study Arm	Part A	Doses in P304 Part A	Part A Dose	Move on to Part B?	Part B	Doses in P304 Part B	Part B B-Dose	Total Doses in P304
Healthy Adult Cohort								
Healthy adults who consent to receive 2 doses in Part A (Days 1 and 29)	**Group A5**	2	100 µg	⇒	**Group B5**	1	100 µg	3

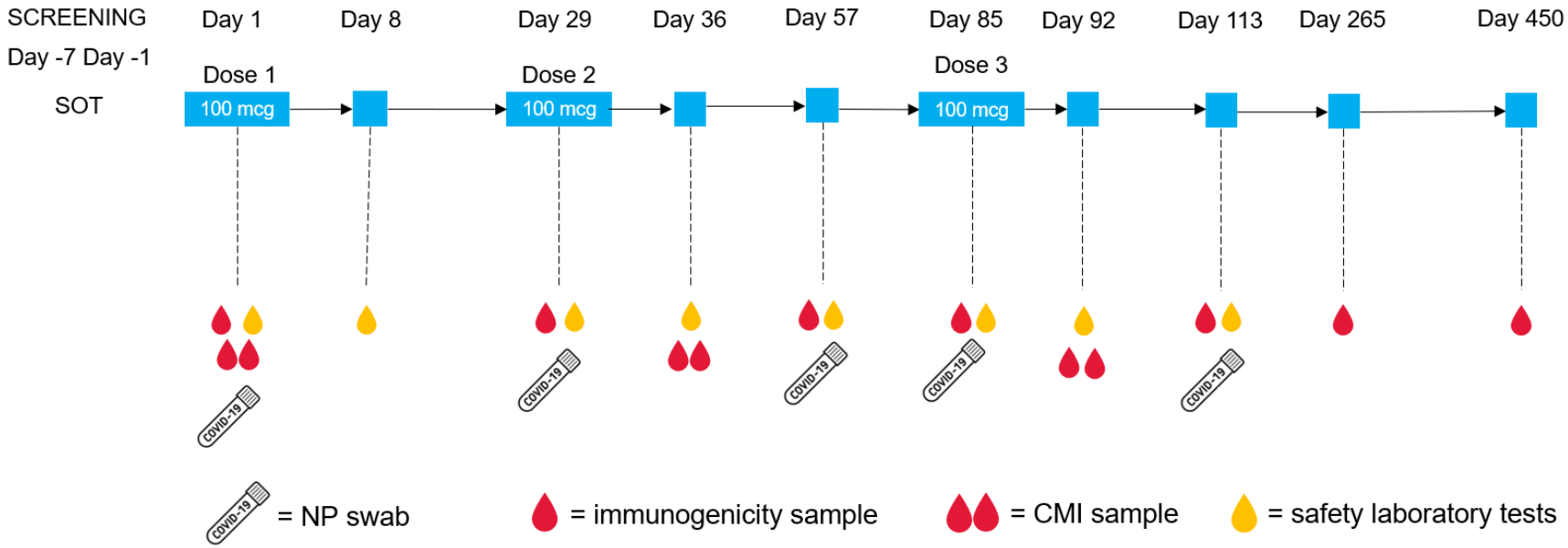
Abbreviations: B-Dose = booster dose; EUA = Emergency Use Authorization; SOT = solid organ transplant,

Figure 1: Study Schema for Unvaccinated Participants Who Receive the 2-Dose Vaccination Regimen (Part A)



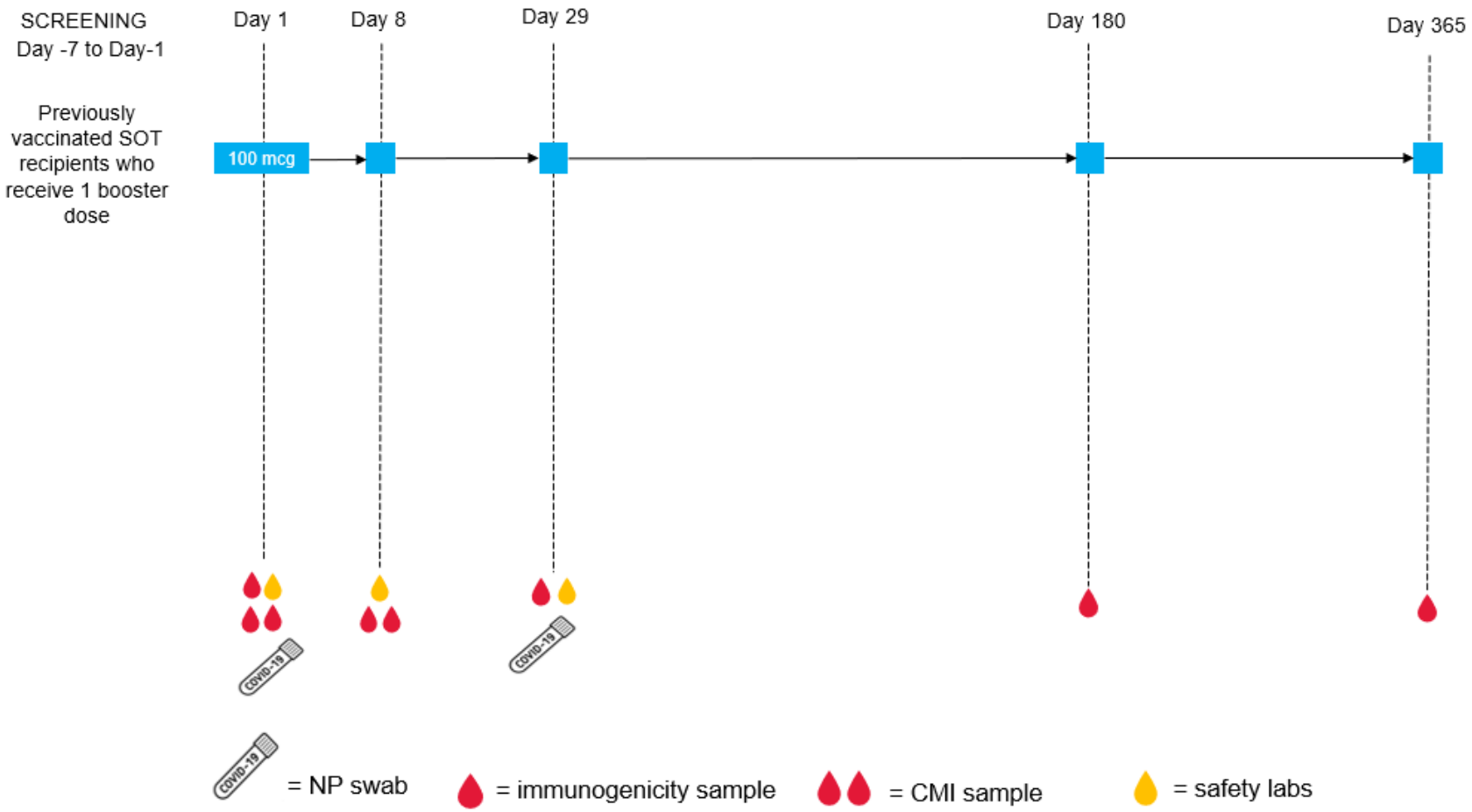
Abbreviations: CMI = cell-mediated immunity; IA = interim analysis; immuno = immunogenicity; NP = nasopharyngeal; SOT = solid organ transplant (recipients).

Figure 2: Study Schema for Unvaccinated Participants Who Receive the 3-Dose Vaccination Regimen (Part A)



Abbreviations: CMI = cell-mediated immunity; NP = nasopharyngeal; SOT = solid organ transplant (recipients).

Figure 3: Study Schema for Previously Vaccinated Participants Who Receive a Single-dose Vaccination Regimen (dose 3) (Part A)



Abbreviations: CMI = cell-mediated immunity; NP = nasopharyngeal; SOT = solid organ transplant.

Figure 4: Booster Phase Study Pathway

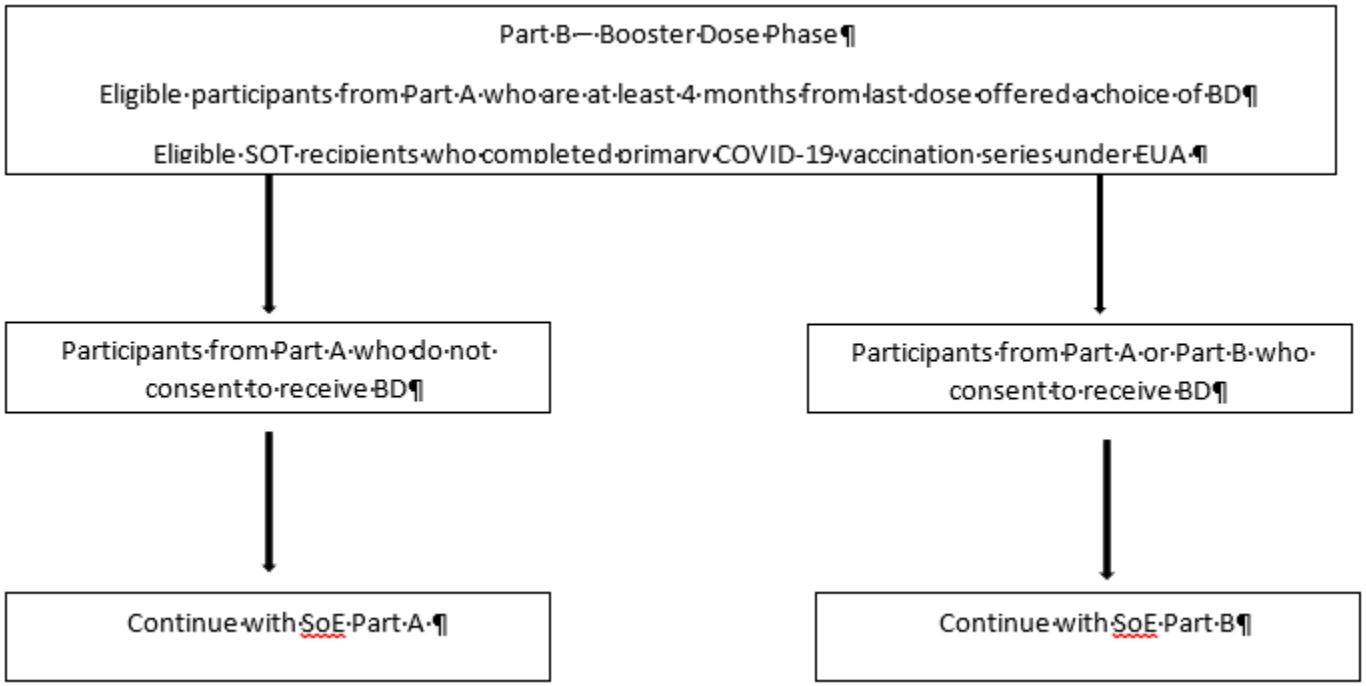
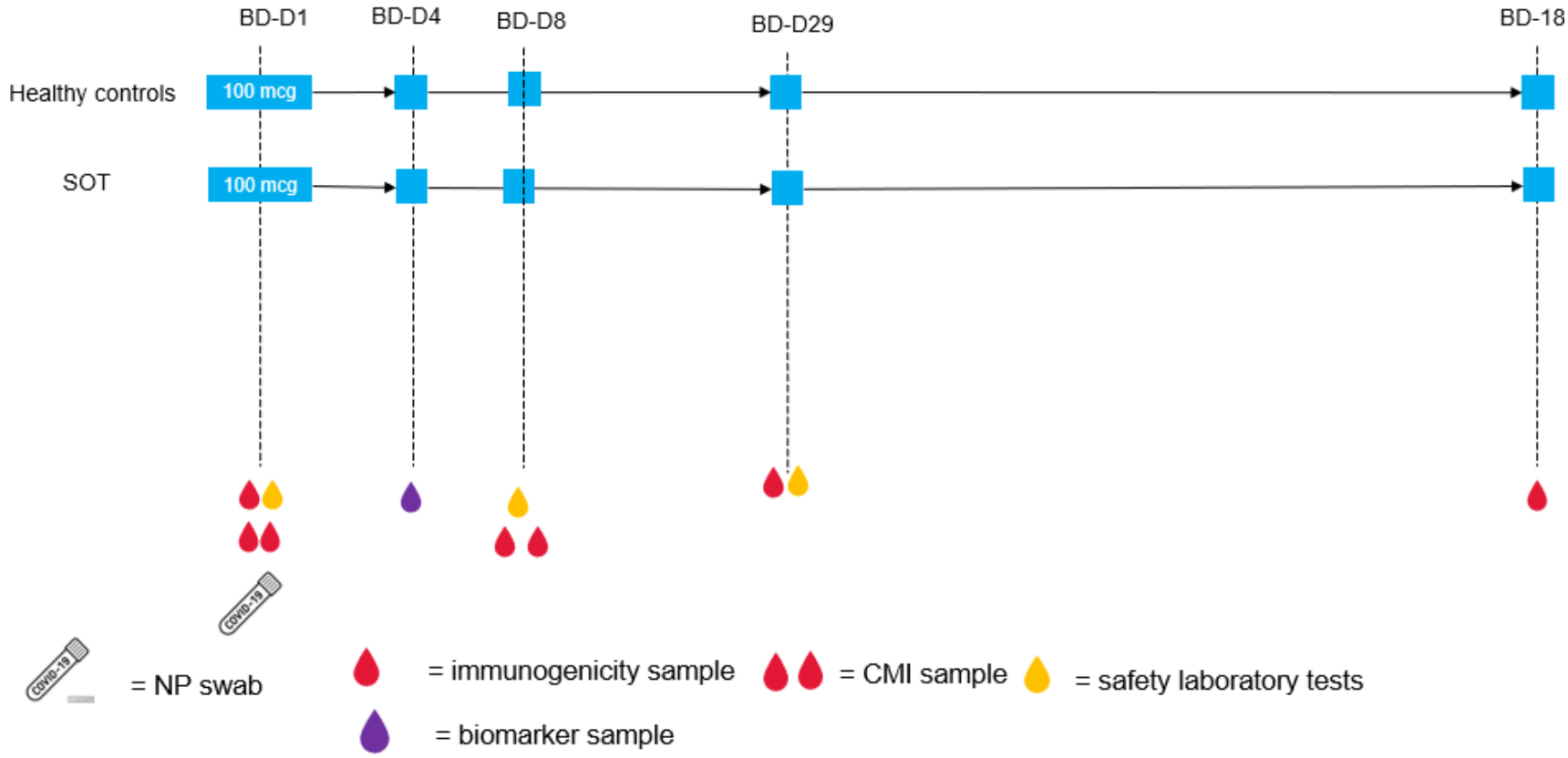


Figure 5: Study Schema for Booster Dose Phase (Part B)



For Part A, the primary immunogenicity goal of the study is to evaluate serum Ab responses obtained 28 days after the second or third dose of vaccine (Day 57 for unvaccinated participants of the 2-dose regimen, Day 113 for unvaccinated SOT participants of the 3-dose regimen, and Day 29 for previously vaccinated SOT participants of dose 3). Using the Ab threshold established from Study P301 (if available at the time of database lock), an additional exploratory analysis will be performed by measuring the proportion of participants with a serum Ab level at Day 57 (for unvaccinated participants of 2-dose regimen), Day 113 (unvaccinated SOT recipients of 3-dose regimen), and Day 29 (previously vaccinated SOT recipients of dose 3) greater than or equal to the Ab threshold of protection against COVID-19, with a 2 sided 95% CI using the Clopper Pearson method by cohort arm.

This study will monitor participants for a total of up to 12 months (12 months after their last dose of vaccine for participants not receiving a BD or 6 months after their BD). The SOT participants who do not consent to receive a third dose of mRNA-1273 (Group A1) and healthy adult participants (Group A5) will be monitored for a total of 12 months after their second dose. Safety assessments will include solicited local and systemic ARs for 7 days after each dose; unsolicited AEs for 28 days after each dose; MAAEs; SAEs; AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal) from dose 1 through the end of study (EOS); concomitant medications associated with AEs, MAAEs, or COVID-19 or SARS-CoV-2 infection; participant experience of COVID-19 symptoms; biopsy-proven organ rejection; safety laboratory assessments; vital sign measurements; and physical examination findings as presented in the applicable SoE (Section 10.1).

From all unvaccinated SOT participants who receive 3 doses of mRNA-1273 (Group A2), blood samples will be collected at baseline (Day 1), Day 29 (28 days after dose 1), Day 57 (28 days after dose 2), Day 85 (dose 3), Day 113 (28 days after dose 3), Day 265 (6 months after dose 3), and Day 450 (12 months after dose 3).

From unvaccinated participants who receive 2 doses of vaccine (healthy adults [Group A5] and SOT recipients who decline to receive a third dose [Group A1]), blood samples will be collected at baseline (Day 1), Day 29 (28 days after dose 1), Day 57 (28 days after dose 2), Day 209 (6 months after dose 2), and Day 394 (12 months after dose 2).

From previously vaccinated SOT participants who receive 1 dose of mRNA-1273 (Group A3), blood samples will be collected at pre-dose 3 (Day 1), Day 29 (28 days after dose 3), Day 180 (6 months after dose 3), and Day 365 (12 months after dose 3).

These blood samples will be for the assessment of the following endpoints and analytes:

- Measurement of SARS-CoV-2-specific bAb and nAb responses

- Development of Ab directed against nonvaccine antigen (nucleocapsid protein), which will signify infection with SARS-CoV-2. Participants who tested positive for Ab against SARS-CoV-2 nucleocapsid protein at baseline can continue in the study.

From unvaccinated SOT participants (Group A1 and Group A2), blood samples for cell-mediated immunity (CMI) studies will also be collected at Day 1, Day 36, and Day 92 (SOT recipients receiving 3 doses [Group A2]) from a subset of at up to 50 SOT participants, as well as, from 20 healthy controls (Group A5) (Day 1 and Day 36), and from a subset of at least 50 previously vaccinated SOT recipients (Group A3) at Day 1 and Day 8, for exploratory assessments to characterize T- and B-cell responses to vaccine.

The NP swab samples obtained at illness visits (Section 7.3.1) will be used as sources of SARS-CoV-2 for genetic sequencing.

SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) will also be collected at the Illness and Convalescent visits.

The number of cases of COVID-19 will be assessed throughout the study (Section **Error! Reference source not found.**). Once a participant is identified as a case of COVID-19, a convalescent visit will be scheduled approximately 28 days after the confirmed diagnosis for a clinical evaluation and immunologic assessment of SARS-CoV-2 infection.

For unvaccinated SOT recipients (Group A1 and Group A2), laboratory assessments for safety related to kidney function for kidney SOT recipients (serum creatinine, urine protein, and UPCR) and liver function for liver SOT recipients (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) will be monitored on Day 1, Day 8, Day 29, Day 36, and Day 57 for SOT recipients who receive 2 doses only (Group A1) and on additional Days 85, 92, and Day 113 for SOT recipients who receive 3 doses (Group A2).

For previously vaccinated SOT recipients (Group A3), laboratory assessments for safety will be monitored on Day 1 (dose 3), Day 8, and Day 29.

After Day 57 (for unvaccinated SOT participants who receive 2 doses [Group A1]) or after Day 113 (for unvaccinated SOT participants who receive 3 doses [Group A2]), or after Day 29 (for previously vaccinated SOT recipients who receive dose 3 [Group A3]), the investigator will review standard-of-care laboratory assessments related to kidney and liver function and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

Part B - Booster Phase

Part B is designed to offer participants in Part A, who are at least 4 months from the last dose, the option to request a BD (100 µg) of the prototype mRNA-1273 (Group B2, Group B3, and

Group B5). Part B is also designed to enroll SOT participants who completed primary vaccination series with mRNA or non-mRNA COVID-19 vaccine under the EUA who are at least 4 months from last dose (Table 3). At least 50 SOT recipients who completed primary vaccination series with a non-Moderna COVID-19 vaccine under the EUA (outside of the mRNA-1273-P304 study) will be enrolled in Part B. In case a variant of concern emerges and available data show a decreased immune response after vaccination with the prototype 100 µg BD, the Part B Booster Phase may test or replace the prototype 100 µg BD with a variant-specific mRNA-1273 vaccine (ie, Omicron-specific or mRNA-1273.529).

Table 3: Primary Series Vaccination for Booster Dose Eligibility

Primary Series Vaccine	Primary Series Number of Doses
mRNA COVID-19 vaccine (ie, Moderna, Pfizer)	3 doses
Non-mRNA COVID-19 vaccine (ie, Janssen)	2 doses or at least 1 dose combined with an mRNA COVID-19 vaccine

If eligible, each study participant in Part A will receive a notification letter and will be asked to schedule a BD-1 visit at their study site. Principal Investigators should consider current local public health guidance for administration of COVID-19 vaccines under EUA and marketing authorization (if any) when determining the scheduling priority of participants.

At the BD-1 visit, each participant will:

- Each study participant in Part A will be encouraged to remain in the ongoing study,
- Sign a revised informed consent form (ICF) that includes both updated safety information relevant to the ongoing study and a BD.
  - Participants from Part A will be offered the option to receive a 100 µg BD (Group B2 and Group B3),
  - Eligible SOT participants who completed the primary vaccination series under EUA will be given a 100 µg BD of mRNA-1273 (Group B4),
  - Under Amendment #4, unvaccinated SOT participants who will be enrolled will be given 3 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose.
  - Under Amendment #4, SOT participants previously vaccinated with 2 doses of Moderna COVID-19 vaccine outside of the study who will be enrolled will receive a third 100 µg dose in Part A then proceed to Part B to receive a 100 µg BD.

- Be counselled about the importance of continuing other public health measures to limit the spread of disease including social distancing, wearing a mask, and hand-washing.

At the BD-1 visit, participants will have the following study site visits and complete scheduled activities according to the Part B SoE:

- BD-1 visit: Participants will receive a single 100 µg dose of mRNA-1273
- BD-1a visit: Day 4, 3 days after BD on Day 1
- BD-2 visit: Day 8, 7 days after BD on Day 1
- BD-3 visit: Day 29, 28 days after the BD on Day 1
- BD-4 visit: Day 181, 180 days after the BD on Day 1

3.1.1. Study Periods

There will be 3 study periods: a Screening Period, a Treatment Period, and a Follow-up Period.

For unvaccinated SOT and Healthy participants who receive the 2-dose vaccine regimen in Part A (Group A1 and Group A5):

The study comprises 8 scheduled visits, including a screening visit and 7 scheduled clinic visits. Electronic diary (eDiary) recording of solicited local and systemic reactogenicity (Section 7.5.3) will occur on the day of each injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363. Additional safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377. If the last dose is delayed, additional safety calls every 4 weeks should be scheduled when the gap between the safety call scheduled on D377 and the last study visit is beyond 28 days.

Per participant, the study duration will be approximately 13 months, which includes 1 week for screening (Day -7 to Day 1), 28 days for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. Day 0 and Day 1 may be combined on the same day (Table 7).

For unvaccinated participants who receive the 3-dose vaccine regimen in Part A (Group A2):

The study comprises 11 scheduled visits, including a screening visit and 10 scheduled clinic visits. eDiary recording of solicited local and systemic reactogenicity (Section 7.5.3) will occur on the day of each injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 127 to Day 239 and again from Day 279 to Day 419. Additional safety follow-up via a safety telephone call will be performed every

4 weeks from Day 141 to Day 253 and again from Day 293 to Day 433. If the last dose is delayed, additional safety calls every 4 weeks should be scheduled when the gap between the safety call scheduled on D433 and the last study visit is beyond 28 days.

Per participant, the study duration will be approximately 15 months, which includes 1 week for screening (Day -7 to Day 1), 3 months for dosing (on Day 1, Day 29, and Day 85), and 12 months of follow-up after the third dose to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. Day 0 and Day 1 may be combined on the same day (Table 8).

For previously vaccinated participants who receive the single-dose vaccination regimen (dose 3) in Part A (Group A3):

The study comprises 6 scheduled visits, including a screening visit and 5 scheduled clinic visits. eDiary recording of solicited local and systemic reactogenicity (Section 7.5.3) will occur on the day of injection and for 6 days following injection. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 43 to Day 155 and again from Day 194 to Day 306. Additional safety follow-up via a safety telephone call will be performed every 4 weeks from Day 57 to Day 169 and again from Day 208 to Day 320.

Per participant, the study duration will be approximately 12 months, which includes 1 week for screening (Day -7 to Day 1), and 12 months of follow-up after dose 3 to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19. The screening visit and Day 1 may be combined on the same day (Table 9).

For participants who receive the BD in Part B (Group B2, Group B3, Group B4, and Group B5):

The study comprises 5 scheduled clinic visits and 6 safety calls (BD-D15, BD-D22, BD-D59, BD-D89, BD-D119, and BD-D149).

Per healthy participant receiving 2 doses of mRNA-1273 in Part A (Group B5) who consent to receive BD, the study duration will be approximately 10 months, which includes 1 week for screening (Day -7 to Day 1), 4 months for dosing (on Day 1, Day 29, and Day 129 for BD), and 6 months of follow-up after the BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who received 3 doses of mRNA-1273 in Part A (Group B5) who consent to receive BD, the study duration will be approximately 13 months which includes 1 week for screening (Day -7 to Day 1), 7 months of dosing (on Day 1, Day 29, Day 85, and Day 205 for BD) and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who previously received 2 doses under EUA, enrolled in Part A to receive a third dose (Group B3) and who consent to receive a BD, the study duration will be approximately 10 months which includes 1 week for screening (Day -7 to Day 1), 4 months of dosing (Day 1 [dose 3] and Day 120 [BD]) and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Per SOT study participant who previously completed primary vaccination series (3 doses) under EUA (Group B4), the study duration will be approximately 6 months which includes 1 week for screening (Day -7 to Day 1), 1 day for dosing and 6 months of follow-up after BD to monitor for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements (Section 10.2.1).

3.1.1.1. Screening Period

The Screening Period for each participant starts with the first screening visit (Day 0) and ends with the Day 1 visit; the Screening Period can last up to 7 days. After signing the informed consent form, participants will undergo screening assessments to determine study eligibility. Screening assessments must be completed after signing the informed consent form (ICF). The investigator will review study entry criteria to determine the participant eligibility during the Screening Period.

Participants deemed eligible will enter the Treatment Period.

3.1.1.2. Treatment Period and Follow-up Period

The Treatment Period for each participant starts with Day 1 and is scheduled to end 28 days after each dose of vaccine. In Part A, for unvaccinated SOT and healthy participants who receive the 2-dose regimen (Group A1 and Group A5), the Follow-up Period starts with Day 58 and is scheduled to end on Day 394 (12 months after the second dose). The Follow-up Period for unvaccinated SOT participants who receive the 3-dose regimen (Group A2) starts with Day 114 and is scheduled to end on Day 450 (12 months after the third dose). The Follow-up Period for previously vaccinated participants (Group A3) starts with Day 29 and is scheduled to end on Day 365 (12 months after dose 3). In Part B (Group B2, Group B3, Group B4, and Group B5), Follow-up Period starts with Day 29 and is scheduled to end on BD-D181 (6 months after BD).

For Part A (Group A1, Group A2, Group A3, and Group A5): On Day 1, after the completion of the scheduled assessments (Section 10.1), all participants will be administered a single IM dose of 100 µg of mRNA-1273 (Section 5.3.2). Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. For unvaccinated SOT and healthy participants (Group A1, Group A2, and Group A5), the second dose of vaccine will be administered on Day 29. Unvaccinated SOT recipients who consent to receive a third dose of

vaccine (Group A2) will receive it on Day 85. Previously vaccinated SOT recipients (Group A3) will receive dose 3 on Day 1. Participants will be monitored for 12 months after the second and third dose (as applicable) of vaccine for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

For Part B (Group B2, Group B3, Group B4, and Group B5): On BD-D1, after the completion of the scheduled assessments, at least 4 months after the last dose, all participants will be administered a single intramuscular (IM) dose of 100 µg BD of mRNA-1273. Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. Participants will be monitored for 6 months after the BD for safety, immunogenicity, and breakthrough SARS-CoV-2 infection or COVID-19.

Testing and assessments for SARS-CoV-2 infection and COVID-19 are detailed in Section 7.1.6. Scheduled testing for the presence of SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) will occur after collecting nasopharyngeal (NP) swab samples on each day of injection. In Part A, on Day 1, Day 29, and Day 85 before dosing as well as on Day 57 (28 days after the second dose for unvaccinated SOT and healthy participants [Group A1 Group A2, and Group A5]), Day 113 (28 days after the third dose for unvaccinated SOT participants [Group A2]), and on Day 29 (28 days after dose 3) for previously vaccinated SOT recipients [Group A3], and in Part B (Group B2, Group B3, Group B4, and Group B5), on BD-D1 before dosing. During the Treatment Period and Follow-up Period, participants who meet prespecified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment, including an NP swab sample to be tested for the presence of SARS-CoV-2 by RT-PCR (Section 7.1.6). Confirmed, symptomatic cases of SARS-CoV-2 infection will be captured as MAAEs (Section 7.3.2).

Blood Samples for Immunogenicity Assessment:

All participants will be monitored for safety and reactogenicity and provide pre- and post-dose blood specimens for immunogenicity through 12 months after additional primary dose (dose 3 [Group A3]) and second (Group A1) and third (Group A2) (as applicable) doses of mRNA-1273 (Part A) and through 6 months after BD Group B2, Group B3, Group B4, and Group 5). Blood sampling for immunogenicity testing is scheduled throughout the study as follows:

- For unvaccinated SOT and healthy participants who receive the 2-dose regimen on Day 1 and Day 29, as well as well as 28 days and 6 and 12 months after the second dose (Part A, Group A1 and Group A5),
- For unvaccinated SOT participants who receive the 3-dose regimen on Day 1, Day 29, Day 57, and Day 85, as well as 28 days and 6 and 12 months after the third dose (Part A, Group A2), and

- For previously vaccinated SOT participants who receive dose 3 on Day 1 and Day 29 (28 days after dose 3), as well as 6 and 12 months after dose 3 (Part A, Group A3).
- For participants in Part B (participants in Part A who consented to receive a BD [Group B2, Group B3, and Group B5] and SOT participants who completed the primary vaccination series under EUA who receive a BD [Group B4]), on BD-D1, BD-D-29, and BD-D181.

Blood Samples for CMI Analysis:

Part A

For unvaccinated SOT participants (Group A1 and Group A2), blood samples will also be collected for CMI analysis at Day 1, Day 36, and Day 92 (SOT recipients who receive a third dose [Group A2]) from a subset of up to 50 SOT participants, as well as, from 20 healthy controls (Day 1 and Day 36) (Group A5).

Blood samples will also be collected from a subset of at least 50 previously vaccinated SOT recipients (Group A3) for CMI analysis at Day 1 (dose 3) and Day 8 (7 days after dose 3).

Part B

For participants in Part B (participants in Part A who consented to receive a BD [Group B2, Group B3, and Group B5] and SOT participants who completed the primary vaccination series under EUA who receive a BD [Group B4]), blood samples will be collected for CMI analysis at BD-D1 and BD-D8 (7 days after BD) from all Part B participants.

Blood and urine samples for kidney and liver function

Blood and urine samples related to kidney (kidney SOT) and liver function (liver SOT) will be monitored on:

Part A

- Day 1, Day 8, Day 29, Day 36, and Day 57 for unvaccinated SOT recipients who receive 2 doses only (Group A1) and on additional Days 85, 92, and 113 for unvaccinated SOT recipients receiving 3 doses (Group A2).
- On Day 1, Day 8, and Day 29 for previously vaccinated SOT recipients who receive dose 3 (Group A3).
- After Day 57 (for unvaccinated SOT recipients receiving 2 doses) [Group A1], after Day 113 (for unvaccinated SOT recipients receiving 3 doses [Group A2]), or after Day 29 (for previously vaccinated SOT recipients who receive dose 3 [Group A3]), the investigator

will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

Part B

- On BD-D1, BD-D8, and BD-D29 for SOT participants who completed primary vaccination series (Group B2, Group B3, and Group B4): After Day 29, the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

Blood samples for biomarker analysis:

During BD-D4 (Part B of the study [Group B2, Group B3, Group B4, and Group B5]), participants who chose to receive a BD will have blood draws (biomarker plasma and biomarker serum samples) which will be stored for potential future biomarker assessment.

Participants will be instructed on the day of the first dose and reminded on the days of the second, third, and fourth doses (as applicable) how to document and report solicited local or systemic ARs in a provided eDiary. Solicited ARs, unsolicited AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), and biopsy-proven organ rejection will be assessed as described in Section 7.1, according to the time points in the applicable SoE (Section 10.1).

Participants may experience and report AEs that necessitate an unscheduled visit. At the discretion of the investigator, additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

3.2. Scientific Rationale for Study Design

The study vaccine, mRNA-1273, is currently being evaluated in a pivotal Phase 3 efficacy, safety, and immunogenicity study in an adult population at high risk of COVID-19 disease (Study P301). Success criteria for early efficacy were met at first interim analysis based on 95 adjudicated cases with a vaccine efficacy of 94.5% (95% CI: 86.5%, 97.8%; one-sided p value < 0.0001). Immunocompromised individuals were excluded from this study.

The current study aims to describe the safety and Ab responses elicited following the last dose of vaccine among adult kidney and liver transplant recipients evaluated against the Ab responses of healthy adult participants in this study and in Study P301 (if available at the time of database lock). This study is expected to provide initial clinical information whether vaccination with mRNA-1273 can induce vaccine response in this population of immunocompromised participants, and whether 3 doses of vaccine induces a greater response than a 2-dose regimen. Recent data based

on post-EUA experience show that solid organ transplant recipients' response to mRNA-based COVID-19 vaccines were substantially lower compared to what has been reported in the general population with antibody responses detectable in only 30-60% after 2 doses (Benotmane et al 2021; Boyarsky et al 2021b, Grupper et al 2021; Marinaki et al 2021).

A small case series which evaluated the antibody responses and vaccine reactions in 30 solid organ transplant recipients who had suboptimal response to standard vaccination show that SOT recipients who had low-positive antibody response before the third dose had high-positive antibody titers after dose 3 and some of those who had negative antibody response had either low- to high-positive antibody response after dose 3 (Werbel et al 2021).

In addition, a recently published article described a double-blind, randomized, controlled trial of a third dose of mRNA-1273 vaccine (Moderna) as compared with placebo (NCT04885907; Hall et al 2021). The results demonstrated that a third dose of mRNA-1273 vaccine in transplant recipients elicited a substantially higher immune response than placebo, as determined in the analysis of both primary and secondary trial endpoints. The third dose was considered safe when risk versus benefit was considered.

Administration of additional vaccination is a strategy shown to improve immune response to viral antigens based on clinical experiences with hepatitis B and influenza vaccines (Nevens et al 2006; Natori et al 2018).

Interim data are available from an ongoing Moderna Phase 2 study, mRNA-1273-P201 (Study P201) where healthy adult participants in Study mRNA-1273-P201 received 2 doses of either 50 µg or 100 µg of mRNA-1273 and were administered a 50 µg booster of mRNA-1273 6 to 8 months after the second dose. Participants in mRNA-1273-P201 who received the BD, demonstrated enhanced immune responses to SARS-CoV-2 compared to pre-boost levels and met the noninferiority criteria stipulated in the US Food and Drug Administration Guidance on EUA for Vaccines to Prevent COVID-19. Available data also show that heterologous or mixed series of COVID-19 vaccine induced high immune response in the adult population (Atmar et al 2021). Additionally, no new safety signals emerged upon administration of the BD in Study P201. In addition, interim results from the mRNA-1273-P205 study show that the currently authorized 50 µg booster of mRNA-1273 increased neutralizing antibody levels against Omicron approximately 37-fold compared to pre-boost levels and a 100 µg dose of mRNA-1273 increased neutralizing antibody levels approximately 83-fold compared to pre-boost levels. Based on cumulative evidence, the benefit-risk profile of a BD of mRNA-1273 is favorable, particularly in light of increasing breakthrough disease with the emergence of the Delta variant. Providing the option for a BD to all eligible participants currently enrolled in the study as well as enrolling eligible SOT recipients who completed primary vaccination series under EUA is expected to

generate valuable homologous and heterologous booster data in the immunocompromised population.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre- and post-dose blood samples for Ab analysis through 12 months after the last dose of vaccine in Part A or through 6 months after the BD in Part B. In addition, in Part A, unvaccinated participants will have NP swab samples collected, before the injections on Day 1 and Day 29, and on Day 57 for those receiving the 2-dose regimen, before injections on Day 1, Day 29, and Day 85,and on Day 57, and Day 113 for those receiving the 3-dose regimen, and before injection on Day 1 and on Day 29 for previously vaccinated SOT recipients who receive dose 3. In Part B, NP swabs will be collected before BD injection on BD-D1. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasal or NP swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and RT-PCR. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

As it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the NP and/or nasal swab samples collected before study injection and the serologic assays for Ab responses to nonvaccine antigen(s) may help discriminate between natural infection and vaccine-induced Ab responses, should such discrimination be needed.

3.3. Justification for Dose and Choice of Study Population

The 100 µg dose level is currently being investigated in a large Phase 3 efficacy study in adults 18 years of age and older (Study P301). The 50 µg BD level is currently being investigated in a Phase 2 study in adults 18 years of age and older (P201). Interim results from the mRNA-1273-P205 study show that the 100 µg BD had robust GM titers against the Omicron variant, which were higher numerically than what were observed for the 50 µg BD. Therefore, based on this study and the results of the studies described in Section 1.2.2, the Sponsor intends to study a single-dose level of 100 µg mRNA-1273 primary series and single 100 µg BD in this Phase 3b study in an adult immunocompromised population.

There is no placebo treatment arm for this study. On 18 Dec 2020, the US FDA issued an EUA for the Moderna mRNA-1273 COVID-19 vaccine to be distributed in the US for use in individuals 18 years of age and older (FDA 2020) in response to the ongoing pandemic. On 12 Aug 2021, the US FDA issued an extension of the EUA for a third dose of Moderna mRNA-1273 COVID-19 vaccine in certain immunocompromised individuals, specifically, SOT recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise (FDA 2021). Recent US CDC guidance recommends a COVID-19 BD in people aged ≥ 18 years who are moderately and severely immunocompromised which includes SOT recipients (CDC

2021c). Accordingly, the inclusion of a placebo treatment group would be inappropriate. Instead, an open-label study was designed which intends to enroll adult SOT recipients (kidney and liver transplants) and healthy adults. Participants in the transplant cohort are therapeutically immunosuppressed to avoid transplant rejection. The healthy cohort serves as a concurrent nonimmunosuppressed comparison group for the analysis of cellular immune response.

3.4. End of Study Definition

The EOS for the full study is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the applicable SoE (Section 10.1) for the last participant in this study.

4. STUDY POPULATION

Participants will be enrolled at ~20 US and non-US sites

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

Inclusion and exclusion criteria are listed separately for the SOT recipients (Section 4.1) and for healthy adults (Section 4.1.2).

4.1. Eligibility Criteria (Part A)

4.1.1. Eligibility Criteria for Transplant Recipients (Group A1, Group A2, and Group A3)

4.1.1.1. Inclusion Criteria for Transplant Recipients

Each participant must meet all of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent (Day 0), is EITHER a kidney or liver (single organ) transplant recipient who is at least 90 days after transplantation at the time of consent, and is EITHER:

a. Unvaccinated, or

b. Previously vaccinated with 2 doses of Moderna COVID-19 vaccine who is at least 1 month after the second dose at the time of consent. Participants who received the 2 doses of Moderna COVID-19 vaccine before transplant are not eligible.

2. Received chronic immunosuppressive therapy for the prevention of allograft rejection for a minimum of 90 days before signing consent, including but not limited to: glucocorticoids (eg, prednisolone), immunophilin binding agents (eg, calcineurin inhibitors, mTOR inhibitors), or inhibitors of de novo nucleotide synthesis (eg, mycophenolic acid, mizoribine, leflunomide, azathioprine).

3. Understands, agrees, and is able to comply with the study procedures and provides written informed consent.

4. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

   - Has a negative pregnancy test at Screening and on the day of the first dose (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)

- Has agreed to continue adequate contraception through 3 months following the second dose (Day 29) for those receiving 2-dose regimen, through 3 months following the third dose (Day 85) for those receiving 3-dose regimen, and through 3 months following the third dose (Day 1) for those previously vaccinated SOT recipients
- Is not currently breastfeeding

See Section 10.3, Appendix 3 for Contraceptive Guidance.

5. Is medically stable, according to investigator's judgment, during the 3 months before signing consent. Medically stable is defined as having no significant worsening of a medical condition requiring medical intervention (eg, hospitalization, change in medical therapy).

4.1.1.2. Exclusion Criteria for Transplant Recipients

Participants who meet any of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration or any known history of SARS-CoV-2 infection or positive SARS-CoV-2 test.
2. Is pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the screening visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Has prior or planned administration of a coronavirus vaccine (eg, SARS-CoV-2 [for unvaccinated participants only], SARS-CoV, or MERS-CoV vaccine).
5. Has current treatment with investigational agents for either prophylaxis against COVID-19 (for unvaccinated participants only) or treatment of COVID-19 (eg, anti-SARS-CoV-2 monoclonal antibodies).
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - A history of more than 1 solid organ transplanted (eg, kidney and pancreas). A history of previous kidney or liver transplant is acceptable.

- A history of clinically relevant donor-specific Ab.
- A history of complications of immunosuppression; for example, the following:
  - Hypogammaglobulinemia and post-transplant lymphoproliferative disorders
  - Cytomegalovirus viremia or BK viremia within 1 month of informed consent
- Active infection at the time of consent
- A history of biopsy-proven T-cell or Ab-mediated rejection within 3 months of informed consent, or suspected active or chronic rejection according to the investigator's judgment
- Suspected clinically relevant active hepatitis, including viral hepatitis, according to the investigator's judgment
- Bleeding disorder that is considered a contraindication to IM injection or phlebotomy
- Dermatologic conditions that could affect local solicited AR assessments
- Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients
- Known human immunodeficiency virus infection

8. Has received:
   a. Any nonstudy vaccine within 28 days before or after any dose of vaccine (except for seasonal influenza vaccine, which is not permitted within 14 days before or after any dose of vaccine)
   b. Intravenous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to Day 1
   c. Therapies that have depleting properties on T-cells, B-cells, and plasma cells (examples of depletional therapies include, but are not limited to, antithymocyte globulin, monoclonal antibodies, and proteosome inhibitors) within the last 3 months prior to enrollment
9. Participated in an interventional clinical study within 28 days prior to Day 0 or plans to donate blood products while participating in this study.
10. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

4.1.2. Eligibility Criteria for Healthy Adults (Group A5)

4.1.2.1. Inclusion Criteria for Healthy Adults

Each participant must meet all of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent (Day 0), and is in good general health without current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition, according to investigator assessment, at the time of consent, and has not been vaccinated with any COVID-19 vaccine at the time of consent.
2. Understands, agrees, and is able to comply with the study procedures and provides written informed consent.
3. 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 Screening and on the day of the first dose (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)
   - Has agreed to continue adequate contraception through 3 months following the second dose (Day 29)
   - Is not currently breastfeeding

See Section 10.3, Appendix 3 for Contraceptive Guidance

4. Is medically stable, according to investigator's judgment, during the 3 months before signing consent. Medically stable is defined as having no significant worsening of a medical condition requiring medical intervention (eg, hospitalization, change in medical therapy).

4.1.2.2. Exclusion Criteria for Healthy Adults

Participants who meet any of the following criteria at the screening visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration or any known history of SARS-CoV-2 infection or positive SARS-CoV-2 test.
2. Is pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the screening visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Has prior or planned administration of a coronavirus vaccine (eg, SARS-CoV-2, SARS-CoV, or MERS-CoV vaccine).

5. Has current treatment with investigational agents for either prophylaxis against COVID-19 or treatment of COVID-19 (eg, anti-SARS-CoV-2 monoclonal antibodies).
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
   - Active infection at the time of consent
   - Bleeding disorder that is considered a contraindication to IM injection or phlebotomy
   - Dermatologic conditions that could affect local solicited AR assessments
   - Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients
   - Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.
8. Has received:
   - Any nonstudy vaccine within 28 days before or after any dose of vaccine (except for seasonal influenza vaccine, which is not permitted within 14 days before or after any dose of vaccine)
   - Intravenous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to Day 1
   - Systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent)
9. Participated in an interventional clinical study within 28 days prior to Day 0 or plans to donate blood products while participating in this study.
10. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

4.2. Study Eligibility Criteria (Part B)

4.2.1. Inclusion Criteria (Group B2, Group B3, Group B4, and Group B5)

1. a. Participants must have been previously enrolled in the mRNA-1273-P304 study, are actively participating in Part A and are at least 4 months from the last dose, or

   b. Is an adult male or female individual, at least 18 years of age at the time of signing informed consent, is EITHER a kidney or a liver (single organ) transplant recipient who

is at least 90 days after transplantation at the time of consent AND who completed primary vaccination series (3 doses for mRNA COVID-19 vaccine; 2 doses for non-mRNA COVID-19 vaccine or at least 1 dose of non-mRNA combined with 1 dose of mRNA COVID-19 vaccine) under the EUA who are at least 4 months from the last dose. All primary COVID-19 vaccination series must be completed after transplant.

2. Female participants of childbearing potential may be enrolled in the study if the participant has a negative pregnancy test on the day of the booster dose injection (BD-Day 1).

4.2.2. Exclusion Criteria (for Participants who Completed Primary Vaccine Series under EUA) (Group B4)

Exclusion Criteria in Part A will apply except prior or planned administration of a coronavirus vaccine and current treatment with investigational agents for either prophylaxis against COVID 19.

4.3. Lifestyle Restrictions

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

4.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently given dose 1 of study vaccine and are not allowed to continue to participate in the study. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria, and information on any SAE that may have occurred from Day 1 to the time of withdrawal.

5. STUDY TREATMENT

5.1. Investigational Product Administered

The term vaccine refers to 100 µg mRNA-1273 primary series vaccine and 100 µg mRNA-1273 BD vaccine in this study. Each dose, regardless of the regimen (single-dose, 2-dose, or 3-dose 100 µg mRNA-1273), administered in the study will be 100 µg mRNA-1273. No placebo will be administered during this study.

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2, formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM 102; cholesterol; 1,2 distearoyl sn glycero-3 phosphocholine; and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000. Vaccine is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

5.2. Randomization and Stratification

This is an open-label, single treatment study: there is no randomization. An interactive response technology system will be used to sequentially assign a unique participant identification number within each cohort of the study (transplant recipient cohort or healthy comparison cohort).

Approximately 240 adult participants (220 unvaccinated or previously vaccinated participants who received two 100 µg doses of the Moderna COVID-19 vaccine who have had a kidney or liver transplant and 20 healthy adults) will be enrolled and vaccinated; there will be no stratification or enrollment in blocks. At least 50 SOT recipients who completed primary vaccination series with a non-Moderna COVID-19 under EUA (outside of the mRNA-1273-P304 study) will be enrolled in Part B.

5.3. Dosing and Management of mRNA-1273 Vaccine

5.3.1. Preparation of Study Vaccine for Injection

Each dose of vaccine will be prepared for each participant as detailed in the mRNA1273P304 Pharmacy Manual. For Part A, the volume of vaccine injected will be 0.5 mL, containing a 100 µg dose of mRNA-1273 as detailed in the mRNA-1273-P304 Pharmacy Manual. For Part B, the booster phase, each injection will have a volume of 0.5 mL and contain mRNA-1273 100 µg as in Part A.

5.3.2. Administration of Study Vaccine

Each unvaccinated SOT and Healthy participant (Group A1Group A2, and Group A5) will receive two 100-µg doses of vaccine by IM injection, 28 days apart (ie, Day 1 and Day 29) into the deltoid

muscle, according to the procedures specified in the mRNA-1273-P304 Pharmacy Manual. Preferably, both doses should be administered into the same nondominant arm. Neither dose should be administered into an arm that contains an arteriovenous fistula. Unvaccinated SOT recipients will be offered to receive a third dose of vaccine (Group A2) on Day 85 (56 days after dose 2). Previously vaccinated SOT recipients (Group A3) will receive a single 100-µg dose (dose 3) on Day 1. In Part B (Group B2, Group B3, Group B4, and Group B5), participants will receive a single 100-µg dose on BD-D1. Under Amendment #4, unvaccinated SOT participants who will be enrolled will be given 3 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose. Under Amendment #4, SOT participants previously vaccinated with 2 doses of Moderna COVID-19 vaccine outside of the study who will be enrolled will receive a third 100 µg dose in Part A then proceed to Part B to receive a 100 µg BD.

At each visit when vaccine is administered, participants will be monitored for a minimum of 30 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic ARs.

Eligibility for a subsequent dose of vaccine will be determined by following the criteria outlined in Section 6.

The study sites 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 participant to a resuscitation area or facility are required.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the vaccine
- Confirming the appropriate labeling of the vaccine, so that it complies with the legal requirements of the United States

The investigator is responsible for acknowledging the receipt of the vaccine by a designated staff member at the study site, including the following:

- Confirming that the vaccine was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the vaccine for use

- Ensuring the appropriate dose level of vaccine is properly prepared using aseptic technique

Further description of the vaccine and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the vaccine are described in the mRNA-1273-P304 Pharmacy Manual.

5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of vaccine. The sterile vaccine is packaged in 10R glass vials with a 6.3-mL or 8.0-mL fill volume. The vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

The vaccine will be packaged and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

5.3.5. Study Vaccine Storage

The Moderna COVID-19 vaccine vials are to be stored in a secure area with limited access and protected from moisture and light until it is prepared for administration (Section 5.3.1). Vials are to be stored frozen between -25°C and -15°C (13°F and 5°F). Unpunctured vials may be stored between 8°C and 25°C (46°F and 77°F) for up to 12 hours. The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup refrigerator. The refrigerators must be connected to a backup generator. In addition, vaccine accountability study 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 vaccine that was not temperature controlled during shipment or during storage. Such vaccine will be retained for inspection by the monitor and disposed of according to approved methods.

5.3.6. Study Vaccine Accountability and Disposal

It is the investigator's responsibility that the vaccine accountability study staff maintain accurate records in a vaccine accountability log of receipt of all vaccine, study site vaccine inventory, vaccine dispensing, vaccine injections, and return to the Sponsor or alternative disposition of used and unused vaccine vials.

A study site monitor will review vaccine accountability during study site visits and at the completion of the study during onsite and/or remote monitoring visits.

Vaccine may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A certificate of destruction must be completed and sent to the Sponsor or designee.

Additional details are found in the mRNA-1273-P304 Pharmacy Manual.

5.4. Study Treatment Compliance

All doses of vaccine will be administered at the study site under direct observation of medically qualified study staff and appropriately recorded (date and time) in the eCRF. Qualified study site staff will confirm that the participant has received the entire dose of vaccine. If a participant does not receive vaccine or does not receive all of the planned doses, the reason for the missed dose will be recorded. Data will be reconciled with study site accountability records to assess compliance.

Participants who miss the second or third dose due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol and their regimen schedule. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second or third dose will remain in the study and complete all safety and immunogenicity assessments required through the participant's last scheduled study visit.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Section 10.1). If a participant does not complete a visit within the time window, that visit will be classified as a protocol deviation. The participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

5.5. Prior and Concomitant Medications

5.5.1. 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. In addition, for previously vaccinated participants, the 2 previous doses of the Moderna COVID-19 vaccine received prior to signing the informed consent will be recorded in the participant's eCRF regardless of the timing.

For SOT recipients, all immunosuppressant medications will be recorded in the eCRF page, 3 months prior to Screening and throughout the study. Any change in the maintenance therapy should be recorded and the reason for the change documented. Changes include any adjustments (temporarily or permanently), addition of new immunosuppressants, or switching from 1

maintenance rejection prophylaxis regimen to another. Reasons for change may include, but are not limited to, per center protocol, drug interaction, toxicity, or treatment or prevention of graft rejection.

5.5.2. Concomitant Medications and Therapies

At each study visit and each safety telephone call, study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All immunosuppressant medications, including but not limited to, glucocorticoids (eg, prednisolone), immunophilin binding agents (eg, calcineurin inhibitors, mTOR inhibitors), and inhibitors of de novo nucleotide synthesis (eg, mycophenolic acid, mizoribine, leflunomide, azathioprine) for 3 months prior to Screening and throughout the study. Any immunosuppressants listed in the exclusion criteria if taken during the study should also be recorded.
- All nonstudy vaccinations administered within the period starting 28 days before the first dose of study vaccine, including seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).
- All concomitant medications and nonstudy vaccinations taken through 28 days after each dose of study vaccine. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or MAAE.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each dose of vaccine, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the post-injection study visits or via other participant interactions (eg, telephone calls).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection 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.

5.5.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analysis

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 eligibility to receive a second or third dose or evaluability in the PP analysis (analysis sets are described in Section 8.2):

- Any investigational or nonregistered product (drug or vaccine) other than the mRNA-1273 vaccine used during the study period
- Any medications listed in the study exclusion criteria (Section 4.1.1.2 and Section 4.1.2.2)
- Immunoglobulins and/or any blood products administered during the study period

5.6. Intervention After the End of the Study

Any SAE occurring after a participant's scheduled EOS and considered to be caused by the vaccine must be reported to the Sponsor.

6. DELAYING OR DISCONTINUING STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

6.1. Criteria for Delay of Vaccine Administration

6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature (oral) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the applicable SoE (Section 10.1), or the participant may be discontinued from dosing at the discretion of the investigator (Section 6.2):

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

Participants with a minor illness without fever, as assessed by the investigator, can be vaccinated. Participants with a fever of ≥ 38.0°C/≥ 100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit if possible or at a time the participant is clinically stable according to the judgement of the investigator.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

6.2. Discontinuing Study Vaccination

Participants can discontinue study injection (ie, refuse the second or third dose) for any reason, without prejudice to further treatment the participant may need to receive.

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant does any of the following:

- Withdraws consent to participate in the study (Section 6.3)
- Becomes pregnant (Section 7.5.5)
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 4.1.1.2 or Section 4.1.2.2)

- Experiences an unsolicited AE (other than reactogenicity) after injection that is considered by the investigator to be related to vaccine (Section 7.5.10) and is assessed as severe (Section 7.5.9)
- Experiences an AE or SAE that, in the judgment of the investigator, requires vaccine withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences a clinically significant change in vital sign measurements or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis (Section 7.5.5) clearly related to vaccine
- Experiences an event that meets the criteria for study pause rules (Section 7.6.2)

The reason(s) for withdrawal from further injection will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the investigator could withhold the second or third dose based on a joint decision of the investigator and the CRO's medical monitor (Section 5.5.2).

Every reasonable attempt will be made to follow-up with participants for safety throughout the entire scheduled study period according to their regimen, even if the participant does not receive the second or third dose or misses 1 or more visits. Unless participants withdraw consent, they are expected to remain in the study and complete all scheduled visits and assessments.

6.3. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol. The statistical management of participant withdrawals is discussed in Section 8.

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

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)
- 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) 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 SAE or AE until resolution of the event.

A participant who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the study 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 (Section 10.2.10).

The Sponsor will continue to retain and use all research data 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)

6.4. 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 study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site staff 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, emails, 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, emails, and certified letters) should be documented in the participant's medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

7. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the applicable SoE (Section 10.1). A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. The study site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Section 10.1. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline assessments provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the applicable SoE.

7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the applicable SoE:

- Solicited local and systemic ARs (Section 7.5.3) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited

ARs will be recorded daily using the eDiary (Section 7.1.1). The definition of AR is presented in Section 7.5.1.

- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 7.5.1.
- MAAEs throughout the study period.
- SAEs throughout the study period.
- AESIs throughout the study period.
- AEs leading to discontinuation from dosing and/or study participation (withdrawal) throughout the study period.
- Biopsy-proven organ rejection throughout the study period. A biopsy report will be needed for documentation.
- Safety laboratory assessments:

  Part A

  – For unvaccinated SOT recipients who receive the 2-dose regimen (Group A1), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, Day 29, Day 36, and Day 57. After Day 57, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

  – For unvaccinated SOT recipients who receive the 3-dose regimen (Group A2), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, Day 29, Day 36, Day 57, Day 85, Day 92, and Day 113. After Day 113, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

  – For previously vaccinated SOT recipients who receive dose 3 (Group A3), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on Day 1, Day 8, and Day 29. After Day 29, the investigator will review standard-of-care

laboratory assessments related to kidney and liver function (as related to the SOT) and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

Part B

– For SOT participants who completed primary vaccination series (Group B2, Group B3, and Group B4), safety laboratory assessments related to kidney (for kidney transplant recipients) and liver function (for liver transplant recipients) will be monitored on BD-D1, BD-D8, and BD-D29. After BD-D29, the investigator will review standard-of-care laboratory assessments related to kidney and liver function, and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.

- Vital sign measurements (Section 7.1.4).
- Physical examination findings (Section 7.1.5).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 7.1.6).
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study (Section 7.5.5).
- Changes in immunosuppressant medications in SOT recipients

7.1.1. Use of Electronic Diaries

At the time of consent, participants must confirm that they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, participants will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 7.5.3) on Day 1.

At each injection visit, participants will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants will record data into the eDiary starting approximately 30 minutes after injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the study site, 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 reactogenicity ARs, as defined in Section 7.5.3, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it is resolved or the next vaccine injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever on the day of injection or for the next 6 days.

The eDiary will be the only source documents allowed for solicited local or systemic ARs (including body temperature measurements). 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 solicited ARs.

Any new safety information reported during safety telephone calls or at study site 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. An event reported in this manner must be described as a solicited event and entered on the solicited AR eCRF.

Study site staff will review eDiary data with participants at visits 7 days after each injection.

In Part A, the eDiary will also be used every 4 weeks to capture the occurrence of AEs, MAAEs, SAEs, AESIs, or AEs leading to discontinuation from dosing and/or study participation (withdrawal) as follows:

- Starting at Day 71 through Day 183 and again starting at Day 223 through Day 363 for unvaccinated SOT and healthy recipients of 2 vaccine doses (Group A1 and Group A5),
- Starting at Day 127 through Day 239 and again Day 279 through Day 419 for unvaccinated SOT recipients of 3 vaccine doses (Group A2), and
- Starting at Day 43 through Day 155 and again starting at Day 194 through Day 306 (previously vaccinated SOT recipients who receive dose 3) (Group A3).

The timing of eDiary prompts and safety calls will not be adjusted when the last dose is delayed. If the last dose is delayed beyond the standard window, the following clinic visits should be adjusted:

For the 2-dose regimen (Group A1 and Group A5), the actual date of the last delayed dose should be used to adjust D36 (7 days after last dose), D57 (28 days after last dose), 6 months visit (180 days after last dose) and 12 months visit (365 days after last dose).

For the 3-dose regimen (Group A2), the actual date of the last delayed dose should be used to adjust dates for D97 (7 days after last dose), D113 (28 days after last dose), 6 months visit (180 days after last dose) and 12 months visit (365 days after last dose).

Additional safety calls every 4 weeks should be scheduled when there is a gap beyond 28 days between the safety call scheduled on D377 (for 2 doses [Group A1 and Group A5]) or D433 (for 3 doses [Group A2]) and the last study visit.

As specified in the applicable SoE, the eDiary will prompt the participant to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since in contact with the study site
- Known close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection
- Any experience of symptoms of COVID-19
- Any MAAEs or SAEs

If an eDiary record results in identification of relevant safety events according to the study period, or of symptoms of COVID-19, a follow-up safety telephone call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 7.1.2) as the procedure for safety follow-up approximately every 4 weeks:

- Starting at Day 85 through Day 197 and again starting at Day 237 through Day 377 for unvaccinated SOT and healthy recipients of 2 vaccine doses (Group A1 and Group A5),

- Starting every 4 weeks from Day 141 through Day 253 and again from Day 293 through Day 433 for unvaccinated SOT recipients of 3 vaccine doses (Group A2), and
- Starting at Day 57 through Day 169 and again starting at Day 208 through Day 320 (previously vaccinated SOT recipients who receive dose 3) (Group A3).

The follow-up eDiary questionnaires and the safety calls conducted by the study staff will occur ~2 weeks apart on a 4 week cycle.

7.1.1.1. Ancillary Supplies for Participant Use

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

7.1.2. Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained study site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. In Part A, safety telephone calls follow a schedule for each participant as indicated in the applicable SoE:

- Every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377 for unvaccinated SOT and Healthy recipients of 2 vaccine doses (Group A1 and Group A5),
- Every 4 weeks from Day 141 to Day 253 and again from Day 293 to Day 433 for unvaccinated SOT recipients of 3 vaccine doses (Group A2), and
- Every 4 weeks from Day 57 through Day 169 and again starting at Day 208 through Day 320 for previously vaccinated SOT recipients who receive dose 3 (Group A3).

The schedule of safety telephone calls will not be adjusted for each participant based on the actual day of the last dose, if delayed. Additional safety calls every 4 weeks should be scheduled when there is a gap beyond 28 days between the safety call scheduled on D377 (for 2 doses [Group A1 and Group A5]) or D433 (for 3 doses [Group A2]) and the last study visit.

In Part B, safety telephone calls will be performed on BD-D15, BD-D22, BD-D59, BD-D89, BD-119, and BD-D149 to collect information about occurrence of AEs, MAAEs (including biopsy-proven organ rejection), SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.5.8).

The participant will be interviewed according to the script about occurrence of AEs, MAAEs (including biopsy-proven organ rejection), SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.5.8). In addition, study personnel will collect information on known participant close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. 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. As noted in Section 7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

7.1.3. Safety Laboratory Assessments

All safety laboratory assessments will be conducted at laboratories local to the study sites. To help monitor for potential event of organ transplant rejection in the SOT recipients, safety laboratory assessments will be performed, including assessments related to kidney and liver function (eg, serum creatinine, urine protein, and UPCR for kidney SOT recipients; and ALT, AST, ALP, and bilirubin for liver SOT recipients) at prespecified study visits. After Day 57 (unvaccinated SOT recipients who receive 2 vaccine doses [Group A1]) or after Day 113 (unvaccinated SOT recipients who receive 3 vaccine doses [Group A2]) or after Day 29 (previously vaccinated SOT recipients who receive dose 3 [Group A3] in Part A or SOT recipients who completed the primary vaccination series who receive BD [Group B4]) in Part B, the investigator will review standard-of-care laboratory assessments related to kidney and liver function (as applicable), and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS. The investigator must review results of safety laboratory assessments as soon as they are available. Schedules of sampling for safety laboratory assessments are presented in the SoEs- (Section 10.1).

A point-of-care urine pregnancy test will be performed at the screening visit (Day 0) and before each dose of vaccine. One pregnancy test is sufficient if Day 0 and Day 1 are combined in the same. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. Pregnancy is one of the exclusion criteria (Section 4.1.1.2 and Section 4.1.2.2) in this study and is a reason for dosing discontinuation (Section 6.2). Appendix 3 (Section 10.3) details the study guidance on contraception.

7.1.4. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points

indicated in the applicable SoE. At dosing visits, vital sign measurements will be collected once before injection and at least 30 minutes after injection (before participants are discharged from the study site).

Febrile participants at dosing visits (fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F) may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

7.1.5. Physical Examinations

A full physical examination, including height and weight, will be performed at Day 1 as indicated in the applicable SoE (Section 10.1). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE. Symptom-directed physical examinations will be performed at other time points.

On each injection day before injection and again 7 days after injection, the arm that received the injection should be examined and the associated lymph nodes must be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Body mass index will be calculated at the screening visit (Day 0) only.

7.1.6. Assessments for SARS-CoV-2 Infection

Study participants will have NP samples collected for SARS-CoV-2 testing by RT-PCR at time points specified in the applicable SoE (Section 10.1). A study illness visit or a consultation will be arranged within 72 hours or as soon as possible to collect an NP or nasal swab sample (NP is preferred) to ascertain the presence of SARS-CoV-2 via RT-PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020a)
- Close contact exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

If the participant had known close contact exposure to COVID-19 (eg, close contact exposure to someone with confirmed COVID-19), it will be captured in the COVID-19 exposure form.

If scheduled, the study illness visit may collect additional clinical information at the investigator's discretion, including but not limited to medical history, physical examination, blood sampling for

clinical laboratory testing, and nasal, saliva, and/or NP swab sampling for viral PCR (including multiplex PCR for respiratory viruses, including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. During this visit, a blood sample will also be collected for immunologic assessment of SARS-CoV-2. All findings will be recorded in the eCRF.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant and the participant's primary care physician of the diagnosis. If the study participant does not have a primary care physician, the investigator will assist them in obtaining one. The participant will also be instructed on infection prevention measures consistent with local public health guidance.

Any confirmed symptomatic SARS-CoV-2 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.2). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection

7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the applicable SoE (Section 10.1): The following analytes will be measured:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum bAb against SARS-CoV-2 spike protein measured by ligand binding assay specific to the SARS-CoV-2 S protein

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Measurement of bAb and nAb levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 10.2.6), 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, additional assay development, and the immune response across CoVs.

7.3. COVID-19 and SARS-CoV-2 Infection

To be considered as a case of symptomatic COVID-19 for the evaluation of the secondary endpoint, the following case definition must be met:

- The participant must have experienced at least TWO of the following symptoms: Fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, or new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Severe COVID-19:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed symptomatic COVID-19 as per the secondary endpoint case definition, plus any of the following:
- Clinical signs indicative of severe systemic illness, respiratory rates ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen < 300 mm Hg, OR
    - Respiratory failure or ARDS (defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic blood pressure < 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR
    - Significant acute renal, hepatic, or neurologic dysfunction, OR
    - Admission to an intensive care unit or death.

The alternative case definition of COVID-19, used for surveillance of COVID-19 symptoms (Section 7.3.1), is defined as the following symptoms: fever (temperature ≥ 38°C/≥ 100.4°F), chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, or diarrhea AND a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.

Death attributed to COVID-19 is defined as any participant who dies during the study with a cause directly attributed to a complication of COVID-19.

Serologic Evidence of SARS-CoV-2 Infection:

Serologic evidence of SARS-CoV-2 infection is defined in participants with negative SARS-CoV-2 at baseline as (Table 1):

- bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that become positive (as measured by Roche Elecsys) counted starting at Day 29 (previously vaccinated SOT recipients who receive dose 3 [Group A3]), Day 57 (unvaccinated participants who receive 2 doses [Group A1]), or at Day 113 (unvaccinated SOT recipients who receive 3 doses [Group A2]), or at BD-D29 (for participants who receive BD), or later.

7.3.1. Surveillance for COVID-19 Symptoms

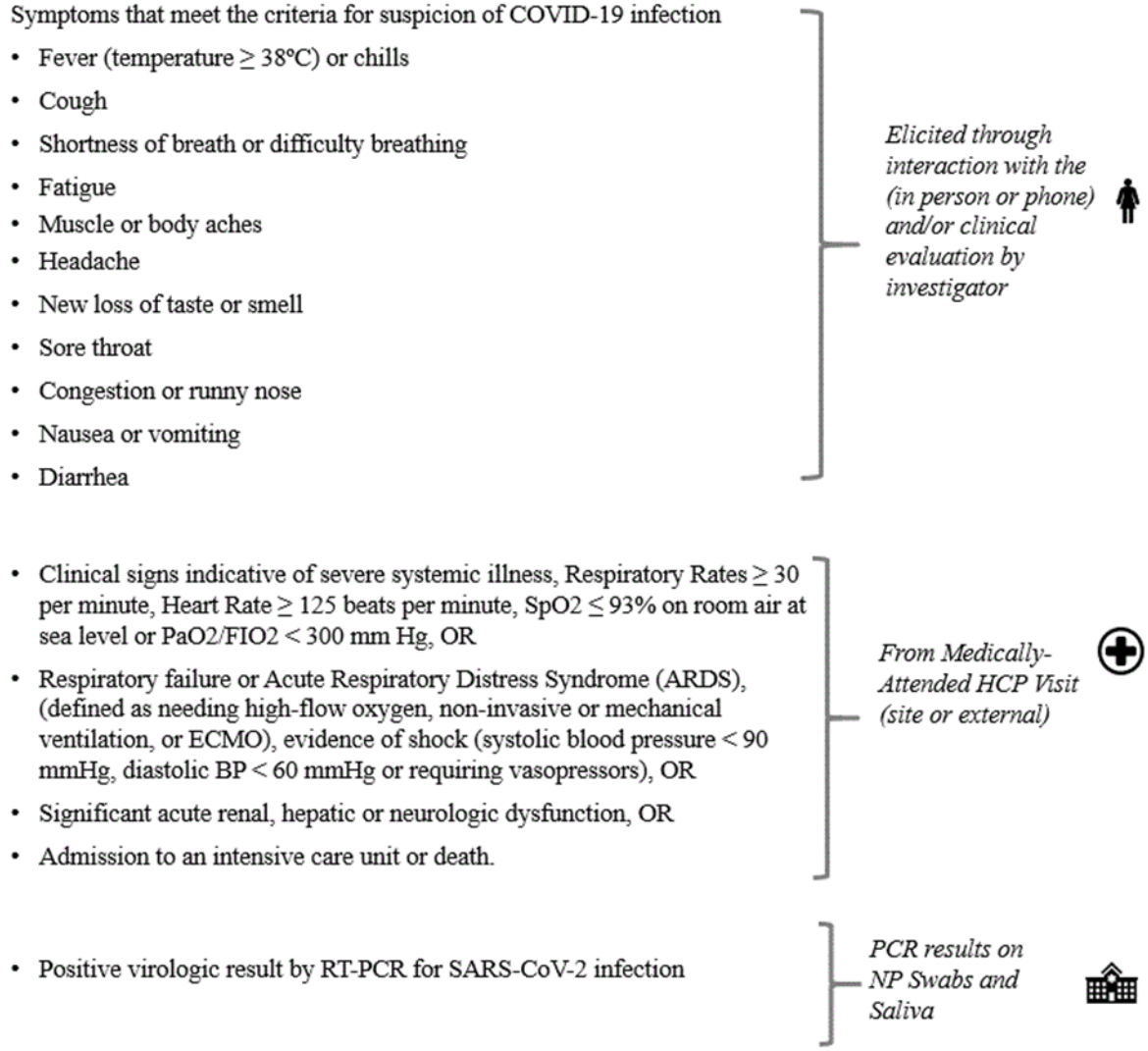
According to the CDC as of 10 Jun 2020 (CDC 2020b), patients with COVID-19 have reported a wide range of symptoms ranging from mild symptoms to severe illness. Throughout the study, to survey for COVID-19, the participant will be instructed to notify the site if the following prespecified symptoms that meet the criteria for suspicion of COVID-19 occur. If any one of these symptoms lasts for at least 48 hours (except for fever and/or respiratory symptoms), the study staff will arrange an illness visit to collect an NP swab within 72 hours:

- Fever (temperature ≥ 38°C/≥ 100.4°F) or chills (of any duration, including ≤ 48 hours)
- Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)
- Cough (of any duration, including ≤ 48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Surveillance for COVID-19 symptoms will also be conducted via eDiary prompts or telephone calls (alternating every 2 weeks) as specified in Section 7.1.1 and Section 7.1.2, respectively.

- For unvaccinated SOT and Healthy participants who receive 2 vaccine doses (Group A1 and Group A5), the eDiary will also be used every 4 weeks, starting at Day 71 through Day 183 and again starting at Day 223 through Day 363. Safety telephone calls will be made every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
- For unvaccinated SOT participants who receive 3 vaccine doses (Group A2), the eDiaries will be collected every 4 weeks starting on Day 127 through Day 239 and again from Day 279 through Day 419. Safety calls will be made every 4 weeks starting on Day 141 through Day 253 and again on Day 293 through Day 433.
- For previously vaccinated SOT participants who receive dose 3 (Group A3), the eDiaries will be collected every 4 weeks starting on Day 43 through Day 155 and again from Day 194 through Day 306. Safety calls will be made every 4 weeks starting on Day 57 through Day 169 and again on Day 208 through Day 320.
- For participants who receive a BD in Part B, safety telephone calls will be performed on BD-15, BD-22, BD-D59, BD-D89, BD-D119, and BD-D149.

Figure 6: Surveillance for COVID-19 Symptoms and the Corresponding Clinical Data Pathways



Abbreviations: BP = blood pressure; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; FIO2 = fraction of inspired oxygen; HCP = healthcare practitioner; NP = nasopharyngeal; PaO2 = partial pressure of oxygen; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SpO2 = oxygen saturation.

It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgment to decide if an NP swab should be collected. The collection of an NP swab prior to the Day 1 and Day 29 vaccinations (for unvaccinated SOT and

healthy participants receiving 2 doses [Group A1 and Group A5]); prior to Day 1, Day 29, and Day 85 vaccinations (for unvaccinated SOT recipients of 3 doses [Group A2]);prior to Day 1 vaccination (for previously vaccinated SOT recipients [Group A3]), and prior to BD-D1 (for participants who receive a BD in Part B) can help ensure that cases of COVID-19 are not overlooked. Any study participant who reports respiratory symptoms during the 7-day period after vaccination should be evaluated for COVID-19.

During the course of the study, participants with symptoms of COVID-19 will be asked to return within 72 hours or as soon as possible to the study site to collect an NP swab sample (for RT-PCR) for evaluation of COVID-19 and collect a blood sample for immunologic assessment of SARS-CoV-2 infection. Both study site visits and telemedicine visits are referred to as illness visits (Section 7.1.6). The NP swab sample will also be tested for the presence of other respiratory infections. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.2). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection. In addition, the study site may collect an additional respiratory sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care.

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. Participants who are hospitalized for COVID-19 without the opportunity for a clinic visit will also be considered cases, assuming that the symptomology criteria for COVID-19 are met and a respiratory sample is positive for SARS-CoV-2 by PCR at a clinical laboratory improvement amendments certified laboratory. Investigators are encouraged to try to obtain a respiratory sample during the course of hospitalization for submission to the study central laboratory, if feasible. The investigator should determine if the criteria for severe COVID-19 have been met.

Severe COVID-19 is defined in Section 7.3.

All clinical findings will be recorded in the eCRF. All confirmed cases of COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be reported immediately to the Sponsor or designee (Section 7.5.4).

7.3.2. Follow-up/Convalescent Period After Diagnosis with COVID-19

Any confirmed COVID-19 occurring in a participant will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic

assessment of SARS-CoV-2 infection. The investigator should determine if the criteria for severe COVID-19 have been met. If the participant is hospitalized, medically qualified study site personnel will try to obtain medical records and SARS-CoV-2 diagnostic results. If the participant is later discharged from the hospital during the 28 day period following diagnosis of COVID-19, the study site personnel will arrange for a resumption of the protocol schedule.

7.4. Exploratory Assessments

Qualitative and quantitative measures of viral load of SARS-CoV-2 will be assessed by RT-PCR of material from NP swab samples obtained at illness visits (Section 7.3.1). Any SARS-CoV-2 genetic sequencing will be performed on the same samples.

In Part A, cellular immune response (eg, markers of CMI, T-cells, and B-cells) will be assessed on Day 1 (before vaccination) and on Day 36 and Day 92 in a subset of at least 50 unvaccinated SOT recipients (kidney or liver) who receive 3 doses (Group A2), from all 20 unvaccinated healthy study participants (Group A5) (Day 1 before vaccination and Day 36), and from a subset of at least 50 previously vaccinated SOT recipients who receive dose 3 (Group A3) (Day 1 before vaccination and Day 8). In Part B Booster Phase, CMI will also be assessed on BD-D1 before vaccination and BD-D8 from all participants in Part B.

Analysis of markers of CMI will be performed in a laboratory designated by the Sponsor.

Blood samples for biomarker analysis will be collected during BD-D4 (Part B of the study [Group B2, Group B3, Group B4, and Group B5]) which will be stored for potential future biomarker assessment.

Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

7.5. Safety Definitions and Related Procedures

7.5.1. Adverse Event

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

Events Meeting the Adverse Event Definition

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

Events NOT Meeting the Adverse Event Definition

- 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 AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 7.5.10). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine and the AE.

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, for the 7 days after each dose of vaccine).

7.5.2. 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 the vaccine.

- **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 1 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.

7.5.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and severity of selected signs and symptoms (ARs) occurring after vaccine injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 7.1.1). Participants will record such occurrences in an eDiary on the day of each dose injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 4 modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next vaccine injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit. All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
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 (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
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

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
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 activity	Requires emergency room visit or 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°C-38.4°C 100.4°F-101.1°F	38.5°C-38.9°C 101.2°F-102.0°F	39.0°C-40.0°C 102.1°F-104.0°F	> 40.0°C > 104.0°F

[a.] Grading for Grade 4 events per investigator assessment (with exception of fever).

Note: Events listed above but starting > 7 days post study injection will be recorded on the Adverse Event page of the electronic case report form. Causality for each event will be determined per assessment by the investigator.

Source: Guidance for industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

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

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP; otherwise meets the definition of an 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 lasting beyond 7 days after injection
- Solicited local or systemic AR that leads to participant withdrawal from vaccine
- Solicited local or systemic AR that otherwise meets the definition of an SAE

7.5.4. Medically Attended Adverse Events

A MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory test results follow-up, COVID-19 [Section 7.3.1]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAE. Unsolicited AEs will be captured on the AE page of the eCRF.

All confirmed COVID-19 cases (Section 7.3.1) will be recorded as MAAEs and reported to the Sponsor or designee immediately and in all circumstances within 24 hours, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.5.12). The investigator will submit any updated COVID-19 case data to the Sponsor within 24 hours of it being available.

7.5.5. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required and documentation is in the form of a case narrative. Such events may require further investigation to characterize and understand them. Refer to Section 10.5, Appendix 5 for a list of AESIs pertinent to this study. 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 (EDC) system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI, and the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.5.12).

Anaphylaxis

All suspected cases of anaphylaxis should be recorded as an AESI, a MAAEs, and reported as SAEs, based on criteria for a medically important event (Section 7.5.2), 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 as per Section 7.5.12 (Reporting SAEs). 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/symptoms consistent with anaphylaxis as shown 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 hypersensitivity reaction with multi-organ-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:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving 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

Acute Myocarditis and/or Pericarditis

All suspected cases of probable or confirmed myocarditis, pericarditis, or myopericarditis should be recorded as an AESI, and reported as an SAE, if the event meets seriousness criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 7.5.12. The investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs/symptoms consistent with the CDC case

definitions as described below (Gargano et al 2021), should be reported as a potential case of confirmed or probable myocarditis, pericarditis, or myopericarditis.

The CDC case definitions are intended to serve as a guide to help in the diagnosis and reporting of suspected cases of myocarditis and/or pericarditis; however, the diagnosis of suspected cases is left to the investigator's clinical judgement.

Acute Myocarditis Case Definition

Presence of ≥ 1 new or worsening of the following clinical symptoms (persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis [probable or confirmed]):

- Chest pain/pressure/discomfort
- Dyspnea/shortness of breath/pain with breathing
- Palpitations
- Syncope

AND

For PROBABLE CASE:

Presence of ≥ 1 new finding of the following:

- Troponin level above upper limit of normal (any type of troponin)
- Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis
    - To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of the following:
        - ST segment or T-wave abnormalities
        - Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias
        - AV nodal conduction delays or intraventricular conduction defects
- Abnormal cardiac function or wall motion abnormalities on echocardiogram
- Cardiac magnetic resonance imaging (cMRI) finding consistent with myocarditis (Ferreira et al 2018)

AND

- No other identifiable cause of the symptoms and findings

For CONFIRMED CASE:

- Histopathologic confirmation of myocarditis (using Dallas criteria [Aretz et al 1987])

OR

- 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

Acute Pericarditis Case Definition

Presence of ≥ 2 new or worsening of the following clinical features (Adler et al 2015):

- Acute chest pain (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 may occur)
- Pericardial rub on examination
- New ST-elevation or PR-depression on EKG
- New or worsening pericardial effusion on echocardiogram or magnetic resonance imaging

Myopericarditis Case Definition

Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis.

7.5.6. Suspected or Confirmed Organ Transplant Rejection

All cases of suspected or confirmed organ transplant rejection must be reported within EDC system as MAAEs. All cases of biopsy-proven organ transplant rejection should be reported as SAEs, based on criteria for a medically important event (Section 7.5.2). As an SAE, the event should be reported to the Sponsor or designee immediately and, in all circumstances, within 24 hours as per Section 7.5.12 (Reporting SAEs). Suspected cases of organ transplant rejection that meet the criteria for SAEs should also be reported as SAEs per the same processes. For confirmed AND suspected cases of organ transplant rejection, the investigator should provide all relevant data (eg, signs and symptoms, associated laboratory tests, diagnostic testing including imaging and procedures, and biopsy results) to the Sponsor within 24 hours of these data being available.

After Day 57 (for unvaccinated SOT recipients of 2 doses [Group A1]), after Day 113 (unvaccinated SOT recipients of 3 doses [Group A2]), or after Day 29 (previously vaccinated SOT

recipients who receive dose 3 [Group A3]) or after BD-D29 for SOT participants who receive a BD [Group B2, Group B3, and Group B4]), the investigator will review the standard-of-care laboratory assessments and report any suspected or confirmed event of organ transplant rejection until the EOS.

7.5.7. Recording and Follow-up of Pregnancy

Female individuals who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with vaccine but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- 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 Sponsor or designee within 24 hours of the study site learning of its occurrence, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.5.12). 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 intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site 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.

7.5.8. Eliciting and Documenting Adverse Events

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 each dose. Other (unsolicited) AEs will be collected from Day 1 through 28 days after each dose.

Both MAAEs and SAEs will be collected from participants as specified in the applicable SoE until the end of their participation in the study. Any AEs that occur before administration of vaccine will be analyzed separately from AEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including COVID-19 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 nonstudy vaccinations.

In addition to participant observations, physical examination findings or data 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, or the participant is LTFU (as defined in Section 6.4).

7.5.9. Assessment of Severity

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 7.5.2), NOT when it is rated as severe.

The severity 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 Preventative 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 7.5.3. Specific criteria for vital signs and laboratory abnormalities are presented in Section 10.4, Appendix 4, and will be graded if outside of the reference range for the laboratory utilized. For laboratory abnormalities not included in the protocol-defined grading system, the guidelines for all unsolicited AEs will be used to describe severity.

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.

Determination of Severe COVID-19 is described in Section 7.3.

Study 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 severity 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.

7.5.10. Assessment of Causality

The investigator's assessment of an AE's relationship to vaccine 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 vaccine 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 vaccine. Participant did not receive the vaccine OR temporal sequence of the AE onset relative to administration of the vaccine is not reasonable OR the AE is more likely explained by another cause than the vaccine.

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

7.5.11. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to vaccine 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 the type of event, time of onset, investigator specified assessment of severity (impact on activities of daily living) and relationship to vaccine, 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.

7.5.12. Reporting SAEs

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

Any AE considered serious by the investigator or that meets SAE criteria (Section 7.5.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE); these include anaphylaxis and confirmed organ transplant rejection. The investigator will assess whether there is a reasonable possibility that the vaccine caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) 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 (USA): +1-866-599-1341
- SAE Fax line (USA): +1-866-599-1342

Regulatory reporting requirements for SAEs are described in Section 7.5.16.

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 vaccine or study procedures, or that caused the participant to discontinue the study.

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

Medical occurrences that begin before the start of vaccine dosing 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.

Adverse events may be collected as follows:

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

Solicited ARs will be collected from the day of injection through 6 days after each dose. Other (unsolicited) AEs will be collected from the day of injection through 28 days after each dose.

SAEs will be collected from the start of vaccine dosing until the last day of study participation.

All SAEs will be recorded and reported to the Sponsor or designee immediately and in all circumstances within 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to dose modification or study drug discontinuation, or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after EOS participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the vaccine or study participation, the investigator must promptly notify the Sponsor.

7.5.14. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and severity 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 suspected causal relationship to vaccine. 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 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 the occurrence of AEs.

7.5.15. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 6.4, including ongoing SAEs after study completion.

7.5.16. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

7.6. Safety Monitoring

The CRO's medical monitor, the Sponsor's medical monitor, and the individual study site investigator(s) will monitor safety throughout the study.

7.6.1. Safety Review Committee

An independent safety review committee (SRC) consisting of transplant nephrologist(s) and hepatologist(s) not involved in the conduct of the study will monitor and adjudicate for events of organ transplant rejection starting from Day 1 and throughout the study period. The SRC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SRC. Details regarding the SRC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

In Part A, the investigator will review laboratory safety assessments of kidney and liver function performed as part of the study at Day 1, Day 8, Day 29, Day 36, and Day 57 for unvaccinated SOT recipients who receive 2 doses (Group A1) and on additional Days 85, 92, and 113 for unvaccinated SOT recipients who receive 3 doses (Group A2), and at Day 1 (dose 3), Day 8, and Day 29 for previously vaccinated SOT recipients (Group A3), for close monitoring around the time of vaccination. In Part B, the investigator will review laboratory safety assessments of kidney and liver function performed as part of the study at BD-D1, BD-D8, and BD-D29. If any of the following criteria are met, the laboratory test(s) must be repeated within 3 days: an increase in serum creatinine ≥ 25% from baseline or increase in UPCR > 0.5 g/g from baseline in kidney SOT

recipients, and an increase in ALT or AST > 3x the baseline in liver SOT recipients. Additional tests may be performed at the discretion of the investigator upon approval of the Sponsor. The investigator should perform a clinical assessment (eg, elicit a history/narrative of the event, perform a physical examination, request diagnostic tests such as imaging or biopsy) of any laboratory abnormality if there is suspicion of an organ transplant rejection. Clinical referral to a transplant specialist for further assessment may be performed by the investigator if needed. A confirmed diagnosis of organ transplant rejection will be based on histologic assessment or tissue biopsy. After Day 57 (unvaccinated SOT recipients who receive 2 doses [Group A1]), after Day 113 (unvaccinated SOT recipients who receive 3 doses [Group A2]), or after Day 29 (previously vaccinated SOT recipients who receive dose 3 [Group A3]) in Part A, or after BD-D29 in Part B Booster Phase, the investigator will review standard-of-care laboratory assessments and report any suspected or confirmed event of organ transplant rejection until the EOS. The investigator or designee is responsible for reporting to the Sponsor, via the EDC system within 24 hours of observation and subsequently routed to SRC for independent review, if any of the following is met:

1. Any of the thresholds for kidney or liver function test is met, confirmed by repeat test, and clinically assessed as suggestive of organ transplant rejection,
2. Any suspected event of organ transplant rejection based on clinically significant kidney or liver function test(s) associated with signs and symptoms suggestive of transplant rejection, or
3. Any report of biopsy-proven organ transplant rejection.

The SRC will assess if the event is a true case of organ transplant rejection. The Sponsor will then make a final decision on whether to suspend further enrollment and/or study dosing based on assessment of the overall potential safety risk to study participants or potential participants who have undergone SOT.

7.6.2. Internal Safety Committee and Study Pause Rules

An internal safety team (IST) will be created specifically to review safety and reactogenicity data after:

- At least 10 SOT recipients have received their third dose of study vaccine and have at least 7 days of reactogenicity data
- At least 55 SOT recipients have received their third dose of study vaccine, unless a safety event requires earlier review
- Any other ad hoc safety concerns based on ongoing safety surveillance

The IST will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the IST. Details regarding the IST composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

Study pause rules will be implemented and will only remain in effect until all study participants who consented to receive a third dose have received their third dose of vaccine. If the following occur, vaccination with third dose may be temporarily suspended until expedited Sponsor review of safety data take place to assess over all potential safety risk to SOT recipients:

- Reactogenicity: Two Grade 4 solicited local or systemic reactogenicities that are related to the vaccine
- Hypersensitivity: Five SOT recipients experiencing a severe systemic allergic reaction that is related to the vaccine
- Adverse Event: Three SAEs or Grade 4 AEs (laboratory and vital sign abnormalities per Section 10.4, Appendix 4 reported as AEs by the investigator) that are related to the vaccine
- Fatal Outcome: One death that is related to the vaccine

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause. The investigator or designee is responsible for reporting to the Sponsor, via the EDC system within 24 hours of observation, each event potentially meeting any pause rule criterion.

7.6.3. Independent Cardiac Event Adjudication Committee

An independent cardiac event adjudication committee (CEAC) that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of “probable” or “confirmed” events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, which will then make a final decision on whether to suspend further enrollment and/or study dosing based on assessment of the overall potential risk to study participants or potential study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

7.7. 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 10.2.8).

7.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

7.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.10. Biomarkers

Immunogenicity assessments are presented in Section 7.2. Blood collection will be performed for future biomarker analysis.

7.11. Health Economics

Health economics are not evaluated in this study.

8. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for 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 statistical methods related to the study objectives after the study has begun but prior to any data unblinding, 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.

This is an open-label study aimed to describe the safety and Ab responses elicited following doses of mRNA-1273 vaccine among SOT recipients compared to the Ab responses of adult healthy participants in this study and Study P301. Using the Ab threshold established from Study P301 (if available at the time of database lock), an additional exploratory analysis will be performed by measuring the number and proportion of participants with a serum Ab level at Day 57 (for unvaccinated participants who receive 2 doses), at Day 113 (for unvaccinated SOT recipients who receive 3 doses), at Day 29 (for previously vaccinated SOT recipients who receive dose 3), and at BD-D29 (for participants who receive a BD in Part B), greater than or equal to the Ab threshold of protection against COVID-19. No formal hypothesis testing will be performed.

Given that the study does not have a concurrent unvaccinated SOT control group, descriptive statistics will be used to present safety data, and no comparisons with the healthy adult participants will be made.

8.1. Sample Size

The study vaccine, mRNA-1273, is currently being evaluated in a pivotal Phase 3 efficacy, safety, and immunogenicity study in an adult population at high risk of COVID-19 disease (Study P301). Success criteria for early efficacy was met at the first interim analysis based on 95 adjudicated cases with a vaccine efficacy of 94.5% (95% CI: 86.5%, 97.8%; one-sided p value < 0.0001 of testing the null hypothesis of VE $\leq 30\%$). Study P301 is expected to provide immunogenicity data by which an Ab threshold of protection against COVID-19 will be estimated.

This current study, which aims to evaluate Ab responses following a second, third, or fourth (booster) dose of mRNA-1273 vaccine among kidney and liver transplant recipients, is expected to provide clinical data to determine whether vaccination with mRNA-1273 will induce vaccine response in this cohort of immunocompromised participants that is comparable to those of the participants in Study P301 and comparable to those of the concurrently assessed cohort of participants in this study with normal immune function.

With 200 SOT participants, if the true AE rate of biopsy-proven organ rejection is 3%, there is approximately >95% probability to observe at least 1 subject reporting such an AE.

The planned sample size of approximately 240 participants (220 unvaccinated or previously vaccinated participants who have had a kidney or liver transplant and 20 unvaccinated healthy participants) who receive 2-dose regimen and 3-dose regimens of 100 µg of mRNA-1273, or 100 µg BD regimen are expected to provide useful estimates of Ab response at Day 29 for previously vaccinated SOT recipients who receive dose 3 in Part A, and Day 113 for unvaccinated SOT recipients who receive the 3-dose regimen, at Day 57 for unvaccinated participants who receive the 2-dose regimen, and at BD-D29 for Part B participants (participants who receive a BD) (primary endpoints), respectively, for comparison to results from Study P301 (if available at the time of database lock). The healthy adult participants will be used primarily as a biological control for the CMI analysis. This study is designed for estimation purposes, and no between-group comparisons are planned.

8.2. Analyses Sets

The analysis sets are defined in Table 5.

Table 5: Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	All participants who received at least 1 dose of vaccine.
Modified Intent-to-Treat Set (mITT)	All participants who have negative SARS-CoV-2 status at baseline, defined as who have a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline.
PP Subset	All participants in the mITT set who receive all planned doses of study vaccination per schedule and have no major protocol deviations that impact key or critical data.
PP Immunogenicity Subset	All participants who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise. The PP Immunogenicity Set will serve as the primary population for the analysis of SARS-CoV-2-specific bAb and nAb immunogenicity data.
Solicited Safety Set	All participants in the FAS who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All participants who receive at least 1 dose of vaccine. The Safety Set will be used for all analyses of safety except for the solicited ARs.

Abbreviations: AR = adverse reaction; bAb = binding antibody; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; vaccine = investigational product.

8.3. Statistical Methods

8.3.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, height, weight, body mass index, date of transplant, type of SOT, type of donor transplant, indication for transplant, ABO blood group status, and relevant medical history) will be summarized by cohort arm (eg, SOT, healthy adult) and by subcohort as applicable (eg, SOT kidney, SOT liver).

Relevant medical history (including prior medications) for SOT recipients may include history of human leukocyte antigen mismatch, induction therapy, panel reactive antibodies, and prior transplant rejection.

Summary statistics (mean, SD for continuous variables, and number and percentage for categorical variables) will be provided.

8.3.2. Safety Analyses

Given that the study does not have a concurrent unvaccinated SOT control group, descriptive statistics will be used to present safety data, and no comparisons with the healthy adult participants will be made.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be summarized by cohort and subcohort arm.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), biopsy-proven organ rejection, safety laboratory assessments, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day Follow-up Period after each dose will be summarized.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), and adjudicated biopsy-proven organ rejection will be summarized. Unsolicited AEs will be presented by MedDRA preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, MAAEs, and adjudicated biopsy-proven organ rejection will be reported in summary tables.

Clinical laboratory data will be summarized by severity for each visit (per Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, DHHS 2007) and as the maximum over all postvaccination visits. Graphical presentations may include box plots and shift plots. Evaluation of clinically significant changes in safety laboratory measurements will be considered independent of the toxicity grading scale.

For all other safety parameters, descriptive summary statistics will be provided, and Table 6 summarizes the analysis strategy for safety parameters. Further details will be described in the SAP.

Table 6: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events
Any solicited AR (overall and by local, systemic)	X
Any unsolicited AE	X
Any SAE	X
Any AESI	X
Any unsolicited MAAE	X
Any adjudicated biopsy-proven organ rejection	X
Any change in immunosuppressant medications	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; MAAE = medically attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

Notes: X = results will be provided. Unsolicited AEs will be summarized by SOC and PT coded by MedDRA.

8.3.3. Immunogenicity Analyses

The SAP will describe the complete set of immunogenicity analyses. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. In Part A, the primary immunogenicity objective of this study is to evaluate serum Ab responses obtained 28 days after the second or third injection of 100 µg mRNA-1273 (Day 57 for unvaccinated participants who receive 2 doses, Day 113 for unvaccinated SOT recipients who receive 3 doses, and Day 29 for previously vaccinated SOT recipients who receive dose 3) in adult kidney and liver transplant recipients. In Part B, the primary immunogenicity objective of this study is to evaluate serum Ab responses obtained 28 days after the BD.

The study will also evaluate Ab responses obtained at Day 29 (28 days after dose 1), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2) for unvaccinated participants who receive the 2-dose regimen; at Days 1, 29, and 85, as well as 28 days and 6 and 12 months after the third dose for unvaccinated SOT recipients who receive the 3-dose regimen; at Day 1 (dose 3)

and Day 29 (28 days after dose 3), as well as 6 and 12 months after dose 3 for previously vaccinated SOT recipients; and at BD-D29 for participants who receive a BD. The results of the study will be described and evaluated against the Ab responses of adult healthy participants in this study and Study P301 (if available at the time of database lock).

Using the Ab threshold established from Study P301 (if available at the time of database lock), an additional exploratory analysis will be performed by measuring the proportion of participants with a serum Ab level at Day 29 (previously vaccinated SOT recipients who receive dose 3), Day 113 (unvaccinated SOT recipients who receive 3-dose regimen), and Day 57 (unvaccinated participants who receive 2 doses) in Part A, and at BD-29 (participants who receive BD)greater than or equal to the Ab threshold of protection against COVID-19, with a 2 sided 95% CI using the Clopper Pearson method by cohort arm.

The GM level of serum Ab with corresponding 95% CI will be provided at each time point by cohort 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. Additionally, the proportion of participants with a 2×, 3×, and 4× rise in GM level from Day 1 will be measured.

All nAb and bAb endpoints (Table 1, Study Objectives and Endpoints) will be summarized at each time point with Day 29 (previously vaccinated SOT recipients who receive dose 3), Day 57 (unvaccinated participants who receive 2 doses), Day 113 (unvaccinated SOT participants who receive 3 doses) and BD-29 (participants who receive BD) as the time points of interest. The GM levels and GMFRs of both nAb and bAb will be provided with corresponding 95% CIs.

Reverse cumulative distribution curves for antibody titers for all time points will be presented.

8.3.4. Incident Cases of COVID-19 After Vaccination

The number and percentage of participants with COVID-19 after vaccination in the SOT recipient and healthy comparison cohorts will be provided. The number and percentage of participants with severe COVID-19 will be provided similarly.

For serologically confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate will be provided by the healthy cohort arm.

As an additional analysis, the number and percentage of participants with symptomatic and asymptomatic COVID-19 or SARS-CoV-2 infection throughout the study will be summarized.

8.3.5. Exploratory Analyses

The magnitude, phenotype, and percentage of cytokine producing S protein-specific T-cells will be summarized in Part A at Day 1, Day 36, and Day 92 for unvaccinated SOT recipients and at Day 1 and Day 8 for previously vaccinated SOT recipients, and at Day 1 and Day 36 for healthy

participants; and at BD-D1 and BD-D8 in Part B. In addition, the magnitude and phenotype of S protein-specific B-cells will be summarized at each timepoint by cohort arm. B-cell receptor sequence analysis to identify representative B-cell clones and associated major antigenic sites and amino acid residues will be described. Details of these exploratory analyses will be described in the SAP before database lock, and additional exploratory analyses may be described in the SAP.

8.3.6. Subgroup Analysis

Subgroup analyses will be performed as described in the SAP.

8.4. Study Analyses

8.4.1. Interim Analyses

An interim analysis of safety and immunogenicity data is planned following Day 57 (28 days after the second dose for unvaccinated participants) in Part A, after Day 29 (28 days after dose 3 for previously vaccinated SOT recipients) in Part A, and at BD-D29 (28 days after BD in participants who receive a BD) in Part B; a CSR will be prepared. An analysis of safety and/or immunogenicity may be performed at the Sponsor's discretion based on the availability of data.

8.4.2. Final Analyses

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

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

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Events

The primary SoEs are presented in Table 8, Table 9, Table 9, and Table 10.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening (Day 0), BD-D1, Day 1, Day 29, or Day 85 (for unvaccinated 3-dose regimen recipients), a telemedicine visit is acceptable if performed by appropriately delegated study site staff (Section 7). If a participant visit to the study site is not possible (with the aforementioned exceptions), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls.

In Part A, if the visit for the second or third dose (Day 29 for healthy participants or Day 85 for unvaccinated SOT recipients) is disrupted and cannot be completed at Day 29 or Day 85 -3/+7 days 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”), the visit window may be extended to Day 29 or Day 85 + 21 days. In Part A, when the extended visit window is used, the remaining study clinic visits should be rescheduled to follow the scheduled inter-visit interval from the actual date of the second (or third) dose. The timing of ediary follow-ups and safety calls will not be adjusted if the last dose is delayed. Additional safety calls every 4 weeks should be scheduled if there is a gap beyond 28 days between the safety call scheduled on D377 (for 2 doses) or D433 (for 3 doses) and the last study visit

Table 7: Primary Schedule of Events for Unvaccinated SOT and Healthy Participants Who Receive the 2-Dose Vaccination Regimen (Part A: Group A1 and Group A5)

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2,3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85 – D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-7		+3	-3/+7	+3	+7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Informed consent form, demographics, concomitant medications, medical history	X											
Review of inclusion and exclusion criteria	X	X										
Physical examination including height and weight[6]	X	X		X		X			X			X
Lymph node assessment[7]		X	X	X	X							
Vital signs[8]	X	X		X		X			X			X
Pregnancy test[9]	X	X		X								
Blood and urine sampling for safety assessments[10]		X	X	X	X	X						
Recording of standard-of-care kidney or liver laboratory -related AEs[11]							X	X	X	X	X	X
Study injection (including 30-minute post-dose observation period)		X		X								
Blood for immunogenicity and assessment of Ab against nonvaccine antigen[12]		X		X		X			X			X
Blood for cell-mediated immunity analysis[13]		X			X							
Nasopharyngeal swab sample for SARS-CoV-2[14]		X		X		X						

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2,3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85 – D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-7		+3	-3/+7	+3	+7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Surveillance for COVID-19/ Illness visit[15]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X
Convalescent visit[16]		X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[17]		X		X								
Review of eDiary data			X		X							
Follow-up eDiary questionnaires							X			X		
Follow-up safety telephone calls[18]								X			X	
Recording of unsolicited AEs		X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[19]		X	X	X	X	X	X	X	X	X	X	X
Recording of AESIs[18]		X	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[19]		X	X	X	X	X	X	X	X	X	X	X
Recording of suspected AND confirmed organ transplant rejection[19]		X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[19]		X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant immunosuppressant medications[20]	X	X	X	X	X	X	X	X	X	X	X	X
Study completion												X

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; bAb = binding antibody; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; IRB = institutional review board; M = month; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SC = safety (telephone) call; SFU = safety follow-up; SOT = solid organ transplant; UPCR = urine protein to creatinine ratio.

Note: In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if performed within the 7-day screening window. Demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (ie, height, weight, body mass index, date of transplant, type of SOT, type of transplant, indication for transplant, ABO blood group status, and relevant medical history) will be collected.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend 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 telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Telemedicine will be permitted for all nondosing visits, with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Telemedicine visits must be permitted by the study site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).
3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 -3/+7 days 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"), the visit window may be extended to Day 29 + 21 days. When the extended visit window is used, the remaining clinic study visits D36 (last dose + 7 days), D57 (last dose + 28 days), 6 month visit (last dose + 180 days), and 12 month visit (last dose + 365 days) should be rescheduled to follow the scheduled inter-visit interval from the actual date of the second dose. The timing of ediary follow-ups and safety calls will not be adjusted. Additional safety calls every 4 weeks should be scheduled if there is a gap beyond 28 days between the last safety call and the last study visit. Participants who agree to receive a booster dose in Part B of the study will follow the schedule of events for Part B (see Table 10).
4. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
6. Physical examination: A full physical examination, including height and weight, will be performed to determine eligibility prior to administration of vaccine dose on Day 1. Body mass index will be calculated only at the screening visit (Day 0). Symptom-directed physical examinations will be performed at Day 29, Day 57, Day 209, and Day 394. Any clinically significant finding identified during a study visit should be reported as an MAAE.
7. On each injection day before injection and again 7 days after injection, the arm that received the injection should be examined and the associated lymph nodes must be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.
8. Vital signs are to be measured pre- and post-dose on days of injection (Day 1 and Day 29). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1, or Day 29 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
9. The pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
10. Samples for safety laboratory assessments (serum creatinine, urine protein, and UPCR for kidney transplant recipients only; ALT, AST, ALP, and bilirubin for liver transplant recipients only) must be collected prior to dosing on Day 1 and Day 29.
11. After Day 57, the investigator will review standard-of-care kidney and liver laboratory assessments and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.
12. Samples for immunogenicity (bAb against SARS-CoV-2 spike protein and neutralizing antibody against SARS-CoV-2) and assessment of SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) must be collected prior to dosing on Day 1, and Day 29.
13. For assessment of cellular immune response, blood samples will be collected on Day 1 (prior to dosing) and Day 36. Note that 20 healthy participants receiving 2-dose regimen will also have blood samples collected at Day 1 (prior to dosing) and Day 36.
14. The NP swab sample will be collected prior to dosing and used to ascertain the presence of SARS-CoV-2 via RT-PCR.

15. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations including blood sample collection for immunologic assessment of SARS-CoV-2 infection (bAb against the nonvaccine antigen [nucleocapsid protein]). If a study site visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
16. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.
17. Diary entries will be recorded by the participant at approximately 30 minutes after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next vaccine injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed either via telephone call or at the following study visit.
18. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
19. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE, confirmed (biopsy-proven) or suspected events of organ transplant rejection, or MAAE will be recorded from Day 1 through the final visit (Day 394).
20. All immunosuppressant medications, for 3 months prior to Screening and throughout the study. Any change in the maintenance therapy should be recorded and the reason for the change documented.
21. Additional safety calls every 4 weeks should be scheduled if the last dose was delayed and there is a gap beyond 28 days between the safety call scheduled on D377 and the last study visit.

Table 8: Primary Schedule of Events for Unvaccinated Participants Who Receive the 3-Dose Vaccination Regimen (Part A: Group A2)

Visit Number	0	1	2	3	4	5	6	7	8	-		9	-		10
Type of Visit	C	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1		M2	M3		M4	eDiary	SC	M9	eDiary	SC	M15
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2,3]	D57[2, 3]	D85[2,3]	D92	D113[2,3]	Every 4 weeks D127 – D239[3, 4]	Every 4 weeks D141 – D253[3, 5]	D265[2, 3]	Every 4 weeks D279– D419[3, 4]	Every 4 weeks D293– D433[3, 5]	D450[2, 3]
Window Allowance (Days)	-7		+3	-3/+7	+3	-3	-3/+7	+3	-3/+7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28/0	7	28	56/0	7	28	-	-	180	-	-	365
Informed consent form, demographics, concomitant medications, medical history	X														
Review of inclusion and exclusion criteria	X	X													
Physical examination including height and weight[6]	X	X		X		X	X		X			X			X
Lymph node assessment[7]		X	X	X	X		X	X							
Vital signs[8]	X	X		X		X	X		X			X			X
Pregnancy test[9]	X	X		X			X								
Blood and urine sampling for safety assessments[10]		X	X	X	X	X	X	X	X						
Recording of standard-of-care kidney or liver laboratory -related AEs[11]										X	X	X	X	X	X
Study injection (including 30-minute post-dose observation period)		X		X			X								
Blood for immunogenicity and assessment of Ab against nonvaccine antigen[12]		X		X		X	X		X			X			X
Blood for cell-mediated immunity analysis[13]		X			X			X							

Visit Number	0	1	2	3	4	5	6	7	8	-		9	-		10
Type of Visit	C	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1		M2	M3		M4	eDiary	SC	M9	eDiary	SC	M15
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2,3]	D57[2, 3]	D85[2,3]	D92	D113[2,3]	Every 4 weeks D127 – D239[3, 4]	Every 4 weeks D141 – D253[3, 5]	D265[2, 3]	Every 4 weeks D279– D419[3, 4]	Every 4 weeks D293– D433[3, 5]	D450[2, 3]
Window Allowance (Days)	-7		+3	-3/+7	+3	-3	-3/+7	+3	-3/+7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28/0	7	28	56/0	7	28	-	-	180	-	-	365
Nasopharyngeal swab sample for SARS-CoV-2[14]		X		X		X	X		X						
Surveillance for COVID-19/ Illness visit[15]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Convalescent visit[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[17]		X		X			X								
Review of eDiary data			X		X			X							
Follow-up eDiary questionnaires										X			X		
Follow-up safety telephone calls[18]											X			X	
Recording of unsolicited AEs		X	X	X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of AESIs[18]		X	X	X	X	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[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of suspected AND confirmed organ transplant rejection[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	0	1	2	3	4	5	6	7	8	-		9	-		10
Type of Visit	C	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1		M2	M3		M4	eDiary	SC	M9	eDiary	SC	M15
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2,3]	D57[2, 3]	D85[2,3]	D92	D113[2,3]	Every 4 weeks D127 – D239[3, 4]	Every 4 weeks D141 – D253[3, 5]	D265[2, 3]	Every 4 weeks D279 – D419[3, 4]	Every 4 weeks D293 – D433[3, 5]	D450[2, 3]
Window Allowance (Days)	-7		+3	-3/+7	+3	-3	-3/+7	+3	-3/+7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28/0	7	28	56/0	7	28	-	-	180	-	-	365
Recording of concomitant medications and nonstudy vaccinations[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant immunosuppressant medications[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion															X

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; bAb = binding antibody; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; IRB = institutional review board; M = month; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SC = safety (telephone) call; SFU = safety follow-up; SOT = solid organ transplant; UPCR = urine protein to creatinine ratio.

Note: In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if performed within the 7-day screening window. Demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (ie, height, weight, body mass index, date of transplant, type of SOT, type of transplant, indication for transplant, ABO blood group status, and relevant medical history) will be collected.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend 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 telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Telemedicine will be permitted for all nondosing visits, with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Telemedicine visits must be permitted by the study site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).
3. If the visit for the third dose (Day 85) is disrupted and cannot be completed at Day 85 -3/+7 days 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"), the visit window may be extended to + 21 Day 85. When the extended visit window is used, the remaining clinic study visits D92 (last dose + 7 days), D113 (last dose + 28 days), 6 month visit (last dose + 180 days), and 12 month visit (last dose + 365 days) should be rescheduled to follow the scheduled inter-visit interval from the actual date of the third dose. The timing of ediary follow-ups and safety calls will not be adjusted. Additional safety calls every 4 weeks should be scheduled if there is a gap beyond 28 days between the last safety call and the last study visit. Participants who agree to receive a booster dose in Part B of the study will follow the schedule of events for Part B (see Table 10).

4. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 127 to Day 239 and again from Day 279 to Day 419.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 141 to Day 253 and again from Day 293 to Day 433.
6. Physical examination: A full physical examination, including height and weight, will be performed to determine eligibility prior to administration of vaccine dose on Day 1. Body mass index will be calculated only at the screening visit (Day 0). Symptom-directed physical examinations will be performed at Day 29, Day 57, Day 85, Day 113, Day 265, and Day 450. Any clinically significant finding identified during a study visit should be reported as an MAAE.
7. On each injection day before injection and again 7 days after injection, the arm that received the injection should be examined and the associated lymph nodes must be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.
8. Vital signs are to be measured pre- and post-dose on days of injection (Day 1, Day 29, and Day 85). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1, Day 29, or Day 85 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
9. The pregnancy test at Screening, Day 1, and before the second and third study injections will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
10. Samples for safety laboratory assessments (serum creatinine, urine protein, and UPCR for kidney transplant recipients only; ALT, AST, ALP, and bilirubin for liver transplant recipients only) must be collected prior to dosing on Day 1, Day 29, and Day 85.
11. After Day 113, the investigator will review standard-of-care kidney and liver laboratory assessments and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.
12. Samples for immunogenicity (bAb against SARS-CoV-2 spike protein and neutralizing antibody against SARS-CoV-2) and assessment of SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) must be collected prior to dosing on Day 1, Day 29, and Day 85.
13. For assessment of cellular immune response, blood samples will be collected on Day 1 (prior to dosing), Day 36, and Day 92 from a subset of at least 50 unvaccinated SOT recipients (kidney or liver).
14. The NP swab sample will be collected prior to dosing and used to ascertain the presence of SARS-CoV-2 via RT-PCR.
15. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations including blood sample collection for immunologic assessment of SARS-CoV-2 infection (bAb against the nonvaccine antigen [nucleocapsid protein]). If a study site visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
16. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.
17. Diary entries will be recorded by the participant at approximately 30 minutes after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next vaccine injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed either via telephone call or at the following study visit.
18. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation (withdrawal), information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
19. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE, confirmed (biopsy-proven) or suspected events of organ transplant rejection, or MAAE will be recorded from Day 1 through the final visit (Day 450).

[20] All immunosuppressant medications, for 3 months prior to Screening and throughout the study. Any change in the maintenance therapy should be recorded and the reason for the change documented.

[21] Additional safety calls every 4 weeks should be scheduled if there is a gap beyond 28 days between the safety call scheduled on D377 (for 2 doses) or D433 (for 3 doses) and the last study visit.

Table 9: Primary Schedule of Events for Previously Vaccinated Participants Who Receive a Single-dose Vaccination Regimen (dose 3) (Part A: Group A3)

Visit Number	0	1	2	3	-		4	-		5
Type of Visit	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1	eDiary	SC	M6	eDiary	SC	M12
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29	Every 4 weeks D43 – D155[3]	Every 4 weeks D57 – D169[4]	D180	Every 4 weeks D194– D306[3]	Every 4 weeks D208– D320[4]	D365[2,3]
Window Allowance (Days)	-7		+3	±3	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28	-	-	180	-	-	365
Informed consent form, demographics, concomitant medications, medical history	X									
Review of inclusion and exclusion criteria	X	X								
Physical examination including height and weight[5]	X	X		X			X			X
Lymph node assessment[6]		X	X							
Vital signs[7]	X	X		X			X			X
Pregnancy test[8]	X	X								
Blood and urine sampling for safety assessments[9]		X	X	X						
Recording of standard-of-care kidney or liver laboratory-related AEs[10]					X	X	X	X	X	X
Study injection (including 30-minute post-dose observation period)		X								
Blood for immunogenicity and assessment of Ab against nonvaccine antigen[11]		X		X			X			X

Visit Number	0	1	2	3	-		4	-		5
Type of Visit	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1	eDiary	SC	M6	eDiary	SC	M12
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29	Every 4 weeks D43 – D155[3]	Every 4 weeks D57 – D169[4]	D180	Every 4 weeks D194– D306[3]	Every 4 weeks D208– D320[4]	D365[2,3]
Window Allowance (Days)	-7		+3	±3	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28	-	-	180	-	-	365
Blood for cell-mediated immunity analysis[12]		X	X							
Nasopharyngeal swab sample for SARS-CoV-2[13]		X		X						
Surveillance for COVID-19/ Illness visit[14]/ Unscheduled visit		X	X	X	X	X	X	X	X	X
Convalescent visit[15]		X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[16]		X								
Review of eDiary data			X							
Follow-up eDiary questionnaires					X			X		
Follow-up safety telephone calls[17]						X			X	
Recording of unsolicited AEs		X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[18]		X	X	X	X	X	X	X	X	X
Recording of AESIs[17]		X	X	X	X	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[18]		X	X	X	X	X	X	X	X	X

Visit Number	0	1	2	3	-		4	-		5
Type of Visit	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0		M1	eDiary	SC	M6	eDiary	SC	M12
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29	Every 4 weeks D43 – D155[3]	Every 4 weeks D57 – D169[4]	D180	Every 4 weeks D194– D306[3]	Every 4 weeks D208– D320[4]	D365[2,3]
Window Allowance (Days)	-7		+3	±3	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	28	-	-	180	-	-	365
Recording of suspected AND confirmed organ transplant rejection[18]		X	X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[18]		X	X	X	X	X	X	X	X	X
Recording of concomitant immunosuppressant medications[19]	X	X	X	X	X	X	X	X	X	X
Study completion										X

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; bAb = binding antibody; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; IRB = institutional review board; M = month; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; SC = safety (telephone) call; SFU = safety follow-up; SOT = solid organ transplant; UPCR = urine protein to creatinine ratio.

Note: In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if performed within the 7-day screening window. Demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (ie, height, weight, body mass index, date of transplant, type of SOT, type of transplant, indication for transplant, ABO blood group status, and relevant medical history) will be collected.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend 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 telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Telemedicine will be permitted for all nondosing visits, with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Telemedicine visits must be permitted by the study site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee). Participants who agree to receive a booster dose in Part B will follow the schedule of events for Part B (see Table 10).
3. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 43 to Day 155 and again from Day 194 to Day 306.
4. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 57 to Day 169 and again from Day 208 to Day 320.

5. Physical examination: A full physical examination, including height and weight, will be performed to determine eligibility prior to administration of vaccine dose on Day 1. Body mass index will be calculated only at the screening visit (Day 0). Symptom-directed physical examinations will be performed at Day 29, Day 180, and Day 365. Any clinically significant finding identified during a study visit should be reported as an MAAE.
6. On the injection day before injection and again 7 days after injection, the arm that received the injection should be examined and the associated lymph nodes must be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.
7. Vital signs are to be measured pre and post-dose on days of injection (Day 1). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
8. The pregnancy test at Screening and Day 1 (if on separate days) will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
9. Samples for safety laboratory assessments (serum creatinine, urine protein, and UPCR for kidney transplant recipients only; ALT, AST, ALP, and bilirubin for liver transplant recipients only) must be collected prior to dosing on Day 1.
10. After Day 29, the investigator will review standard-of-care kidney and liver laboratory assessments and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.
11. Samples for immunogenicity (bAb against SARS-CoV-2 spike protein and neutralizing antibody against SARS-CoV-2) and assessment of SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) must be collected prior to dosing on Day 1.
12. For assessment of cellular immune response, blood samples will be collected on Day 1 (prior to dosing), and Day 8 from a subset of at least 50 previously vaccinated SOT recipients (kidney or liver).
13. The NP swab sample will be collected prior to dosing and used to ascertain the presence of SARS-CoV-2 via RT-PCR.
14. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations including blood sample collection for immunologic assessment of SARS-Co-V2 infection (bAb against the nonvaccine antigen [nucleocapsid protein]). If a study site visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
15. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.
16. Diary entries will be recorded by the participant at approximately 30 minutes after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved; capture of details of ARs in the eDiary should not exceed 28 days after vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed either via telephone call or at the following study visit.
17. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from dosing and/or study participation withdrawal, information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant close contact exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
18. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after injection; all concomitant medications relevant to or for the treatment of an SAE, confirmed (biopsy-proven) or suspected events of organ transplant rejection, or MAAE will be recorded from Day 1 through the final visit (Day 365). In addition, the 2 previous doses of the Moderna COVID-19 vaccine will be recorded in the participant's eCRF regardless of the timing.
19. All immunosuppressant medications, for 3 months prior to Screening and throughout the study. Any change in the maintenance therapy should be recorded and the reason for the change documented.

Table 10: Booster Dose Phase (Part B: Group B2, Group B3, Group B4, and Group B5)

Visit Number	BD-1	BD-1a	BD-2	-	BD-3	-	BD-4
Type of Visit	C	C	C	SC	C	SC	C
Study Visit Day	BD-D1[1] (D205 for SOTr who received 3 doses; D120 for SOTr who received 1 dose; D149 for healthy cohort; at least 4 mos from last dose for SOTr who received primary series under EUA)	BD-D4	BD-D8	14 and 21 days after BD-D1 (BD-D15, BD-D22)	BD-D29	BD-D59, BD-D89, BD-D119, BD-149	BD-D181
Window Allowance (Days)	- 14 days	-2	+3	+3	-3/+14	+3	-3/+14
Days Since Most Recent Vaccination (in Part B)	0	3	7	-	28	-	180
Informed consent form, demographics, concomitant medications, medical history	X						
Review of inclusion and exclusion criteria	X						
Physical examination including height and weight[2]	X				X		X
Lymph node assessment[3]	X		X				
Vital signs[4]	X		X		X		X
Pregnancy testing[5]	X						
Immunogenicity Assessment							
Blood for immunologic analysis and assessment of Ab against nonvaccine antigen[6]	X				X		X

Visit Number	BD-1	BD-1a	BD-2	-	BD-3	-	BD-4
Type of Visit	C	C	C	SC	C	SC	C
Study Visit Day	BD-D1[1] (D205 for SOTr who received 3 doses; D120 for SOTr who received 1 dose; D149 for healthy cohort; at least 4 mos from last dose for SOTr who received primary series under EUA)	BD-D4	BD-D8	14 and 21 days after BD-D1 (BD-D15, BD-D22)	BD-D29	BD-D59, BD-D89, BD-D119, BD-149	BD-D181
Window Allowance (Days)	- 14 days	-2	+3	+3	-3/+14	+3	-3/+14
Days Since Most Recent Vaccination (in Part B)	0	3	7	-	28	-	180
CMI							
Blood for cell-mediated immunity analysis[7]	X		X				
Biomarker Assessment							
Blood sample for potential biomarker analysis[8]		X					
Blood and Urine Sampling for Safety Assessments[9]	X		X		X		
Recording of standard-of-care kidney or liver laboratory-related AEs[10]						X	X
Dosing							
Study injection (including 30-minute post-dosing observation period[11])	X						
Efficacy Assessment							

Visit Number	BD-1	BD-1a	BD-2	-	BD-3	-	BD-4
Type of Visit	C	C	C	SC	C	SC	C
Study Visit Day	BD-D1[1] (D205 for SOTr who received 3 doses; D120 for SOTr who received 1 dose; D149 for healthy cohort; at least 4 mos from last dose for SOTr who received primary series under EUA)	BD-D4	BD-D8	14 and 21 days after BD-D1 (BD-D15, BD-D22)	BD-D29	BD-D59, BD-D89, BD-D119, BD-149	BD-D181
Window Allowance (Days)	- 14 days	-2	+3	+3	-3/+14	+3	-3/+14
Days Since Most Recent Vaccination (in Part B)	0	3	7	-	28	-	180
Surveillance for COVID-19/Unscheduled Visit[12]	X	X	X	X	X		X
NP swab[13]	X						
Safety Assessments							
Follow-up safety[14]				X		X	
eDiary activation for recording solicited ARs (7 days)[15]	X						
Review of eDiary data[16]			X				
Recording of unsolicited AEs	X	X	X	X	X		
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[17]	X	X	X	X	X	X	X
Recording of AE leading to withdrawal [17]	X	X	X	X	X	X	X
Recording of AESIs[17]	X	X	X	X	X	X	X

Visit Number	BD-1	BD-1a	BD-2	-	BD-3	-	BD-4
Type of Visit	C	C	C	SC	C	SC	C
Study Visit Day	BD-D1[1] (D205 for SOTr who received 3 doses; D120 for SOTr who received 1 dose; D149 for healthy cohort; at least 4 mos from last dose for SOTr who received primary series under EUA)	BD-D4	BD-D8	14 and 21 days after BD-D1 (BD-D15, BD-D22)	BD-D29	BD-D59, BD-D89, BD-D119, BD-149	BD-D181
Window Allowance (Days)	- 14 days	-2	+3	+3	-3/+14	+3	-3/+14
Days Since Most Recent Vaccination (in Part B)	0	3	7	-	28	-	180
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[17]	X	X	X	X	X	X	X
Recording of suspected AND confirmed organ transplant rejection[17]	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[17]	X	X	X	X	X	X	X
Recording of concomitant immunosuppressant medications[18]	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BD = booster dose; C = clinic visit; D = day; eDiary = electronic diary; ICF = informed consent form; MAAE = medically attended AE; NP = nasopharyngeal; SAE = serious adverse event; SC = safety (phone) call; SOTr = solid organ transplant recipients.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor.

1. A BD may be administered to all eligible participants who are currently enrolled in Part A or Part B provided there are no current contraindications for further dosing (Section **Error! Reference source not found.**). A participant who is currently in the Convalescent Period may come in for a BD-1 visit and receive a BD as long they are no longer symptomatic, and this includes the possibility for a Convalescent Visit Day 28 to overlap and be combined with a BD-1 visit. For eligible participants in Part A who are at least 4 months from completion of primary vaccination series who consent to receive BD, the study visit or follow-up 4 months after their last dose in Part A may overlap with BD-D1. In this case, a participant will need to come in for the BD-D1 visit at least 4 months after the last dose and then follow Part B.

2. Symptom-directed physical examination will be performed at the BD-Day 1. At visits BD-2 (BD-D29), and BD-3 (BD-D181), a symptom-directed physical examination may be performed at the discretion of the investigator. Any clinically significant finding identified during a study visit should be reported as a MAAE.
3. On dosing day before injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.
4. Vital signs are to be collected pre- and post-dosing (participant will be seated for at least 5 minutes before all measurements are taken per Section 7.1.4) on the day of injection (BD-D1). Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before dosing (BD-D1) must be rescheduled to receive the injection. Afebrile participants with minor illnesses can be vaccinated at the discretion of the investigator.
5. The pregnancy test at the BD-1 visit will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed.
6. Samples for immunogenicity (bAb against SARS-CoV-2 spike protein and neutralizing antibody against SARS-CoV-2) and assessment of SARS-CoV-2 bAb against the nonvaccine antigen (nucleocapsid protein) must be collected prior to dosing on BD-D1.
7. For assessment of cellular immune response, blood samples will be collected on Day 1 (prior to dosing), and Day 8 from previously vaccinated SOT recipients (kidney or liver).
8. All participants who chose to receive a BD. Serum sample from two ~4 mL blood draws. Biomarker plasma and biomarker serum samples will be stored for potential future biomarker assessment.
9. Samples for safety laboratory assessments (serum creatinine, urine protein, and UPCR for kidney transplant recipients only; ALT, AST, ALP, and bilirubin for liver transplant recipients only) must be collected prior to dosing on BD-D1.
10. After BD-D29, the investigator will review standard-of-care kidney and liver laboratory assessments and report any laboratory-related AEs and suspected or confirmed events of organ transplant rejection until the EOS.
11. Post-dosing, participants will have a 30-minute observation period.
12. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations including blood sample collection for immunologic assessment of SARS-Co-V2 infection (bAb against the nonvaccine antigen [nucleocapsid protein]). If a study site visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
13. The NP swab sample will be collected prior to dosing on BD-D1 and used to ascertain the presence of SARS-CoV-2 via RT-PCR.
14. Trained study personnel will call all participants to collect information relating to any unsolicited AEs, MAAEs (including any signs and symptoms of COVID-19), AESIs, AEs leading to withdrawal, SAEs, information on concomitant medications associated with those events, any nonstudy vaccinations, and any changes in immunosuppressant medications.
15. Diary entries will be recorded by the participant at approximately 30 minutes after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR resolves; capture of details of ARs in the eDiary should not exceed 28 days after vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit.
16. Review of eDiary will occur on BD-D8.
17. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after injection; all concomitant medications relevant to or for the treatment of an SAE, confirmed (biopsy-proven) or suspected events of organ transplant rejection, or MAAE will be recorded from BD-D1 through the final visit (BD-D181). In addition, for SOT participants who completed the primary vaccination series under EUA, the previous doses of the COVID-19 vaccine will be recorded in the participant's eCRF regardless of the timing.
18. All immunosuppressant medications, for 3 months prior to Screening and throughout the study. Any change in the maintenance therapy should be recorded and the reason for the change documented.

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. 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 IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB 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 IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.2.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site, onsite or remotely, to do the following:

- 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, the designated CRO, and the investigator.

According to ICH GCP guidelines, 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, IRB 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 a vaccine 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 vaccine 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 that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the SAE Hotline, and that those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff need information or advice. Visits may occur onsite or remotely depending on the site or state's visitation restrictions.

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct study 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 IRB, or regulatory authorities to inspect the vaccine storage area, vaccine stocks, vaccine records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IRB may visit the study 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 the data were recorded, analyzed, and accurately reported according to the protocol, ICH E6(R2) GCP, 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 IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. 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 required under 21 CFR 54. 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 study site 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 study site are not financially responsible for further treatment of the disease under study.

10.2.5. 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 IRB.

10.2.6. Informed Consent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act, where applicable, and the IRB or study site. All consent documents will be approved by the appropriate IRB. The actual ICF used at each study site may differ, depending on local regulations and IRB requirements. However, all versions of the ICF 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 IRB prior to the ICF 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 them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/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 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 in the study.

The participant must be made aware of, and give consent to, direct access to his/her source medical records by study monitors, auditors, the IRB, 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/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 also explain that excess 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, additional assay development, and the immune response across CoVs.

All participants (healthy and SOT recipients) must sign the most current site-approved ICF.

10.2.7. 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.

IRB approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(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 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 an amendment will be released by the Sponsor, agreed upon by the investigator(s), and approved by the relevant IRB(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 IRB(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 upon by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

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

It is the responsibility of the study site investigator to use continuous vigilance to identify and report protocol deviations to the Sponsor or its designee. All protocol deviations must be addressed in study source documents and reported to study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The study site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2.9. 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 that would make the participant identifiable will not be transferred.

The participant must be informed that his/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/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB 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/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, the relevant regulatory authority, or the IRB.

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.

10.2.10. 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 or antirespiratory 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 Ab-based 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, 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.

10.2.11. 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), as well as some national registries.

In addition, results from clinical trials are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

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

10.2.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the study site under the supervision of the study 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 the 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, IRB 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, CRO).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study 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 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. 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 quality assurance representative from the Sponsor or a 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 onsite inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

10.2.13. 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 study 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 Dictionary.

10.2.14. Source Documents

Source documents are original documents or certified copies and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, 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 study site.

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

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

10.2.15. 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 > 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.

10.2.16. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, 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 participants and should ensure appropriate participant therapy and/or follow-up.

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

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

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

- Continuation of the study represents a significant medical risk to participants

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further mRNA-1273 development

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

10.2.17. 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 study 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 in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

10.3. APPENDIX 3: Contraceptive Guidance

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

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

10.4. APPENDIX 4: Toxicity Grading Scale Tables

Table 11: Severity Grading of Laboratory Abnormalities

Serum Chemistry[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)[b]
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
ALP; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[b] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Table 12: Severity Grading of Vital Sign Abnormalities

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)[b]
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)[b]	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER = emergency room.
Note that fever is classified under systemic reactions for grading purposes.
[a] Participant should be at rest for all vital sign measurements.
[b] When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

10.5. APPENDIX 5: Adverse Event of Special Interest Terms

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in Section 7.5.5. The AESIs in Table 13 are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if any of these events 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 in Table 13.

Table 13: Adverse Events of Special Interest

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset 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 (ARDS)	• Including but not limited to new events of ARDS 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

Medical Concept	Additional Notes
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 etc) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; OR o Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR o Urine volume ≤ 0.5 mL/kg/hour for 6 hours
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 ALT or AST OR o > 2-fold elevation above the upper normal limit for total serum bilirubin or gamma glutamyltransferase or ALP
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 (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed-drug eruptions

Medical Concept	Additional Notes
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or hemolysis, elevated liver enzymes, low platelet count 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 nonhemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per protocol • Follow reporting procedures per protocol
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (includes myalgic encephalomyelitis and Post-Viral Fatigue Syndrome) • Myasthenia gravis

10.6. APPENDIX 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.6.1. Amendment 3: 23 Aug 2021

Amendment 3, 23 Aug 2021

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 enroll participants who had a kidney or liver solid organ transplant (SOT) who previously received 2 doses of mRNA-1273 outside of the study in order for them to receive a third dose as part of the study.

The Summary of Changes table provided below describes the major changes made in Amendment 3 relative to Protocol Amendment 2, including the sections modified and the corresponding rationales. The synopsis of Amendment 3 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 Changes in Protocol Amendment 3

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, Protocol Amendment Summary of Changes, and Header	Updated protocol version and date. Added Protocol Amendment Summary of Changes for Amendment 3 and moved the Summary of Changes for Amendment 2 to Appendix 6: Protocol Amendment History.	To reflect the new version and date of protocol.
Section 1.1 Study Rationale and Section 3.2 Scientific Rationale for Study Design	Added recently published studies to this section.	To reflect the most recent published literature.
Section 1.2.2 Clinical Studies	Added a summary of the ongoing clinical studies in the program.	To align with the current IB.

Section # and Name	Description of Change	Brief Rationale
	Added a reference to the investigator's brochure for the latest safety and efficacy data.	
Section 2 Objectives and Endpoints	The primary immunogenicity endpoint: neutralizing antibody (nAb) titers for 3-dose regimen was moved from a secondary endpoint to a primary endpoint and was also modified to include assessment of immunogenicity from both solid organ transplant (SOT) recipients previously vaccinated with 2 doses of Moderna COVID-19 vaccine under EUA and unvaccinated participants). Reactogenicity in the primary objective was separated out from the safety objective. Additional secondary endpoints were included to reflect the new arm.	To implement the analysis of the new arm (participants who had an SOT who previously received 2 Moderna COVID-19 vaccine doses).
Section 2 Objectives and Endpoints	Day 85 timepoint (dose 3) was added for nAb and binding antibody (bAb) geometric mean titer (GMT) and geometric mean fold rise (GMFR) assessments in the secondary endpoints (for unvaccinated SOT recipients who receive the 3-dose regimen).	To enable longitudinal assessment of changes in nAb and bAb GMT and GMFR relative to dose 3 for unvaccinated SOT recipients who receive the 3-dose regimen. Blood sample collection for immunogenicity assessments are already being collected for Day 85.
Section 3.1 General Study Design	Added a table to represent the study arms and doses.	To increase clarity in the study arms.
Section 3.1 (General Design), Section 3.1.1.2 (Treatment Period and Follow-up Period),	US participants only stipulation for cell-mediated immunity exploratory assessments was removed.	To simplify the protocol because this will be a US only study.

Section # and Name	Description of Change	Brief Rationale
Section 7.4 Exploratory Assessments), and Section 10.1 (Appendix 1: Schedule of Events – Table 6 and Table 7)		
Section 4 Study Population	Removed sites in South America and Europe.	To reflect the appropriate location of the study sites.
Section 4.1.1 Inclusion Criteria for Transplant Recipients	Updated Inclusion Criterion 1 to specifically state unvaccinated or previously vaccinated participants. Updated Inclusion Criterion 4 to clarify that previously vaccinated SOT recipients need to agree to continue adequate contraception "through 3 months following the third dose (Day 1)."	To reflect new amendment to enroll SOT recipients who were previously vaccinated with 2 doses of Moderna COVID-19 vaccine.
Section 4.2.1 Inclusion Criteria for Healthy Adults	Updated Inclusion Criterion 1 to include a clarification that "unvaccinated" healthy participants are eligible to participate in the study.	To clarify that the intent of Inclusion Criterion 1 for healthy adults is to enroll unvaccinated participants.
Section 7.5.4.1 Anaphylaxis	Moved anaphylaxis to Section 7.5.5 Adverse Events of Special Interest.	To improve clarity.
Section 8.4.1 Interim Analyses	Added into the interim analysis assessment of immunogenicity 28 days after dose 3 for previously vaccinated SOT recipients.	To implement the analysis of the new arm (participants who had an SOT who previously received 2 Moderna COVID-19 vaccine doses).
Section 8.4.1 Interim Analyses	Removed the second interim analysis and added text regarding the possibility for another analysis.	To include the possibility for another analysis.
Section 9 (References)	Updated reference list.	To support the text added to the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 10.1 Appendix 1 Schedule of Events Table 6	Deleted "eDiary activation for recording solicited ARs (7 days)" at Day 57.	To correct an error in the protocol.
Section 10.1 Appendix 1 Schedule of Events Table 6	Moved the healthy participant statement for cell immune response (Footnote 13) from Table 7 to Table 6.	To correct an error in the protocol.
Section 10.1 Appendix 1 Schedule of Events Table 7	Added Footnotes "2" and "3" to Day 85 and Day 113. For "Days Since Most Recent Injection" for Day 85, changed from "0" to "Day 56/0". Changed "42" to 42+" For Days Since Most Recent Injection.	To improve clarity.
Section 10.1 Appendix 1 Schedule of Events Table 7	Added "X" to Day 113 for the Convalescent visit.	To correct an error in the protocol.
Section 10.1 Appendix 1 Schedule of Events Table 6, Table 7, and Table 8	Separated lymph node assessment out of the physical examination footnote so it has its own row in each table	To improve clarity.
Global	The protocol was updated throughout to include an additional arm in the study in order to enroll participants who had an SOT (kidney or liver) who previously received 2 Moderna COVID-19 vaccine doses so they can receive a third vaccine dose.	To reflect the new arm (participants who had an SOT who previously received 2 Moderna COVID-19 vaccine doses).

10.6.2. Amendment 2: 28 Jul 2021

Amendment 2, 28 Jul 2021:

This amendment was 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 was to increase awareness of possible cases and to add a case definition for myocarditis and pericarditis as well as guidance for reporting and assessing suspected cases for this study, given the recent reports in the Emergency Use Authorization (EUA) experience of cases with a temporal association between COVID-19 messenger RNA (mRNA) vaccine administration and signs and symptoms of myocarditis and pericarditis.

The Summary of Changes table provided below describes the major changes made in Amendment 2 relative to Protocol Amendment 1, including the sections modified and the corresponding rationales. The synopsis of Amendment 2 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, and new references were added in support of the definition of myocarditis and pericarditis (which did not affect the conduct of the study).

Summary of Changes in Protocol Amendment 2

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, Protocol Amendment Summary of Changes, and header	Updated protocol version and date. Added Protocol Amendment Summary of Changes for Amendment 2 and moved the Summary of Changes for Amendment 1 to Appendix 6: Protocol Amendment History.	Updated to reflect new version and date of protocol.
Section 1.3.2 (Risks to Study Participants and Risk Mitigation)	Added paragraph on rare reports of myocarditis and pericarditis occurring after vaccination with Moderna coronavirus disease 2019 (COVID-19) vaccine under Emergency Use Authorization in adults 18 years and older.	To reflect addendum made to Investigator's Brochure.
Section 3.1 (General Design), Section 3.1.1.2 (Treatment Period and	Removal of 1:1 enrollment of kidney and liver SOT recipients such that the study can enroll kidney or liver SOT recipients	Site projections show higher number of kidney SOT recipients to liver SOT recipients (2:1). It should improve odds of enrolling

Section # and Name	Description of Change	Brief Rationale
Follow-up Period), Section 5.2 (Randomization and Stratification), Section 7.4 Exploratory Assessments), Section 8.1 (Sample Size), and Section 10.1 (Appendix 1: Schedule of Events – Table 6)	until the 220 sample size cap is reached.	quicker if the equal split for enrollment is eliminated.
Section 3.1 (General Design - Figure 2) and Section 10.1 (Appendix 1: Schedule of Events – Table 6)	The Day 85 timepoint was added to describe blood sample collection for immunogenicity and assessment of Ab against nonvaccine antigen. Schedule of Events was corrected by adding 'Blood for immunogenicity and assessment of Ab against nonvaccine antigen" at Day 85.	To correct inconsistency in the protocol. Those participants receiving the 3-dose regimen should have blood drawn for immunogenicity and assessment of Ab against nonvaccine on the day of the third vaccination prior to dosing as stated in footnote 11 of Table 6, protocol synopsis, and protocol Section 3.1.
Section 3.1 (General Design), Section 3.1.1.2 (Treatment Period and Follow-up Period), Section 7.4 Exploratory Assessments), and Section 10.1 (Appendix 1: Schedule of Events – Table 5 and Table 6)	US participants only stipulation was added to describe the cell-mediated immunity exploratory assessments.	To accurately reflect which sites will collect CMI exploratory assessments.
Section 4 (Study Population)	Changed the number of sites from "15-20" to "~20" sites.	To accurately reflect the number of sites.
Section 4.1.1 (Inclusion Criteria for Transplant Recipients)	The inclusion criteria for transplant recipients were previously misnumbered, with a duplicate #2 and duplicate #3. Numbering was corrected to #1 through #7.	To correct an error in numbering.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.2 (Exclusion Criteria for Transplant Recipients)	The exclusion criteria for transplant recipients were previously misnumbered, skipping # 2 and #3. Numbering was corrected to #1 through #10.	To correct an error in numbering.
Section 4.2.2 (Exclusion Criteria for Healthy Adults)	The exclusion criteria for healthy adults were previously misnumbered, with a duplicate #4. Numbering was corrected to #1 through #10.	To correct an error in numbering.
Section 5.3.4 (Study Vaccine Packaging and Labeling)	Added "or 8.0-mL" after "6.3-mL"	To reflect the current fill volume options.
Section 7.5.5 (Adverse Event of Special Interest)	Added CDC case definitions for myocarditis and pericarditis.	To provide guidance to the investigators regarding assessing and reporting myocarditis and pericarditis for this study population.
Section 7.6.2 (Internal Safety Committee and Study Pause Rules)	The study pause rules were clarified as follows: • Grade 3 systemic allergic reaction was intended to have the same severity grading of "severe" as stated in Section 7.5.9 of the protocol; therefore, "Grade 3" was modified to "severe" to maintain consistency of terms in the protocol. • "Definitely or possibly related" was intended to have the same causality assessment of "related" as stated in Section 7.5.10 of the protocol; therefore, "definitely or possibly related" was modified to "related" to	To clarify that Grade 3 systemic allergic reaction was intended to have the same severity grading of "severe" as stated in protocol Section 7.5.9 Assessment of Severity. To clarify that "definitely or possibly related" was intended to have the same causality category of "related" as stated in protocol Section 7.5.10 Assessment of Causality.

Section # and Name	Description of Change	Brief Rationale
	maintain consistency of terms in the protocol. • Reactogenicity was described more clearly to include solicited local and systemic reactogenicity; therefore, "solicited local or systemic" was added. • Grade 4 AE was clarified to refer to the "laboratory and vital sign abnormalities per Section 10.4, Appendix 4"; therefore, a clarificatory sentence in parenthesis "(laboratory and vital sign abnormalities per Section 10.4, Appendix 4 reported as AEs by the investigator)" was added to avoid confusion.	
Section 7.6.3 (Independent Cardiac Event Adjudication Committee)	Added Section 7.6.3, Independent Cardiac Event Adjudication Committee.	To describe the proposed mechanism to assess risk of myocarditis and pericarditis in the study population (to address CBER request to describe how risk of myocarditis and pericarditis will be assessed in the study population receiving mRNA-1273).
Section 8.4.1 (Interim Analyses)	Added the following: A second interim analysis describing safety and immunogenicity data 1 month after dose 3 may also be performed.	To include the possibility for another interim analysis.
Section 9 (References)	Updated reference list.	To support the text added to the protocol for myocarditis and pericarditis.

Section # and Name	Description of Change	Brief Rationale
Section 10.1 (Appendix 1: Schedule of Events – Table 5)	Table 5 Schedule of Events was corrected by removing the pregnancy test at Day 57. Vital signs were separated out from the physical examination row.	A pregnancy test is not warranted as there is no vaccine dose given at this visit. To ensure vital signs were not missed.
Section 10.1 (Appendix 1: Schedule of Events – Table 6)	Participants Who Receive the 3-Dose Regimen on Day 57, Study Visit #5, was corrected by removing an X for eDiary activation. Vital signs were separated out from the physical examination row.	To correct an error in the protocol. There is no need to activate eDiaries at this visit as no vaccine dose is given at this visit. The next timepoint for eDiaries for those receiving the 3-dose regimen is at Day 85, Study Visit #6. To ensure vital signs were not missed.

10.6.3. Amendment 1: 18 Jun 2021

Overall Rationale for the Amendment

The main purpose of this amendment was to change the design so that all the participants who are solid organ transplant (SOT) recipients will be offered the opportunity to receive a third dose of 100 µg mRNA-1273 vaccine on Day 85.

In addition, Amendment 1 incorporated 2 points from the Protocol Clarification Memorandum of 15 April 2021:

- Exclusion criterion #7 is modified to specify that the history of donor-specific antibody be clinically relevant according to the investigator's judgment
- Specified the number of kidney transplant recipients, liver transplant recipients, and healthy controls whose blood would be sampled for assessment of cellular immune response. In addition, due the addition of a third dose, the number of sampling days for cellular immune response is increased to three (Day 1, Day 36, and Day 92); and the number of transplant recipients (55 liver and 55 kidney) and healthy participants (20) with blood sample collection for evaluation of cellular immune response is increased.

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, and new references were added in support of the study rationale (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
Title Page, Protocol Approval Page, and Protocol Amendment Summary of Changes	Updated protocol version and date. Added Protocol Amendment Summary of Changes.	Updated to reflect new version and, date of protocol. A Protocol Summary of Changes section was added to be in line with Moderna guidelines.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The primary safety and reactogenicity objective was revised to specify the evaluation of safety and reactogenicity of both a 2-dose and a 3-dose regimen of mRNA-1273 vaccine.	To implement the analysis of the new, 3-dose vaccination regimen.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The primary immunogenicity objective was revised to reflect a singular time point (Day 57).	To evaluate a singular primary immunogenicity objective.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	A new secondary objective was added, “To evaluate serum neutralizing antibody (nAb) responses to a third dose of 100 µg mRNA-1273.” A new secondary endpoint was added, “The geometric mean titer (GMT) value of SARS-CoV-2-specific nAb level at Day 113.”	To implement the analysis of the new, 3-dose vaccination regimen.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The secondary objectives to evaluate the persistence of the immune response to 100 µg mRNA-1273 assessed by binding antibody (bAb) and nAb levels were revised to add evaluation of 3 doses of 100 µg mRNA-1273 through 1 year after dose 3. Secondary endpoints were revised to add, "The geometric mean (GM) value of anti-SARS-CoV-2 S-specific bAb on Day 1, Day 29 (1 month after dose 1), Day 57 (1 month after dose 2), Day 113 (1 month after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3) Geometric mean fold rise (GMFR) of bAb relative to Day 1 on Day 29 (1 month after dose 1), Day 57 (1 month after dose 2), Day 113 (1 month after dose 3), Day 265 (6 months after dose 3), and Day 450 (1 year after dose 3)".	To implement the analysis of the new, 3-dose vaccination regimen.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	Secondary endpoints for solid organ transplant (SOT) recipients evaluating the incidence of asymptomatic SARS-CoV-2 infection and coronavirus disease 2019 (COVID 19), and the changes in liver and renal function and immunosuppressant medications after vaccination with mRNA-1273 were revised to include endpoints after the third dose in addition to the endpoints after the second dose.	To implement the analysis of the new, 3-dose vaccination regimen.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 2 (Objectives and Endpoints)	Exploratory endpoints measuring T-cell and B-cell responses by flow cytometry in a subset of participants were revised to increase the number of sampling days to three (Day 1, Day 36, and Day 92), to clarify the subset of participants as SOT recipients who receive 3 doses of mRNA-1273.	To implement the analysis of the new, 3-dose vaccination regimen.
Protocol Synopsis and Section 3.1 (General Design), 3.1.1 (Study Periods), 3.1.1.2 (Treatment Period and Follow-up Period), 5.3.2 (Administration of Study Vaccine), 10.1 (APPENDIX 1: Schedules of Events)	The General Design, Study Periods, Treatment Period and Follow-up Period, Administration of Study Vaccine, and schedules of events were updated to include participants who receive the 3-dose vaccine regimen. An additional schedule of events was added for the 3-dose regimen.	To implement the addition of a 3-dose vaccination regimen.
Protocol Synopsis and 4.1.1 (Inclusion Criteria for Transplant Recipients)	Inclusion criterion #2 was modified to specify that receipt of chronic immunosuppressive therapy for the prevention of allograft rejection be for a minimum of 6 months before signing consent.	For consistency with inclusion criterion #1 which specifies enrollment of kidney or a liver (single organ) transplant recipient who is at least 6 months after transplantation at the time of consent.
Protocol Synopsis and 4.1.2 (Exclusion Criteria for Transplant Recipients)	Exclusion criterion #7 was modified to specify that the history of donor-specific antibody be clinically relevant according to the investigator's judgment.	To clarify the intent of exclusion criterion #7.
Protocol Synopsis and 7.4 (Exploratory Assessments)	Specified the number of kidney transplant recipients (55), liver transplant recipients (55), and healthy controls (20) whose blood would be sampled for assessment of cellular immune response. In addition, due the addition of a third dose, the number of sampling days for cellular immune response is increased to three (Day 1, Day 36, and Day 92).	Amended the number of participants whose blood would be sampled and implemented the addition of a 3-dose vaccination regimen.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 7.6.2 (Internal Safety Committee and Study Pause Rules)	Added a description of the internal safety team (IST) and added study pause rules to monitor safety and reactogenicity of 3-dose regimen in SOT recipients: Reactogenicity: Two Grade 4 reactogenicities that are definitely or possibly related to the vaccine Hypersensitivity: Five SOT recipients, experiencing a Grade 3 systemic allergic reaction that is definitely or possibly related to the vaccine Adverse Event: Three SAEs or Grade 4 AEs that are definitely or possibly related to the vaccine Fatal Outcome: One death that is definitely or possibly related to the vaccine.	To describe the IST and study pause rules.
Section 10.1 (Table 6) and Section 10.2.6	Added an informed consent form to be completed by SOT participants who agree to receive a third dose of vaccine.	To implement the addition of a 3-dose vaccination regimen.

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