ModernaTX, Inc.

Protocol mRNA-1273-P304

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

Statistical Analysis Plan

SAP Version 2.0
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List of Abbreviations

Abbreviation	Definition
Ab	antibody
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
BMI	body mass index
BP	blood pressure
CI	confidence interval
COVID-19	coronavirus disease 2019
DHHS	Department of Health and Human Services
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
FIO2	fraction of inspired oxygen
GM	geometric mean
GMFR	geometric mean fold rise
GMC	geometric mean concentration
GMR	geometric mean ratio
IgG	immunoglobulin G
IP	investigational product
LLOQ	lower limit of quantification
LOD	limit of detection
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mRNA	messenger ribonucleic acid
MSD	Meso Scale Discovery
nAb	neutralizing antibody
NP	nasopharyngeal
PaO2	partial pressure of oxygen
PCR	polymerase chain reaction
PP	per-protocol
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
S	Spike
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus
SD	standard deviation
SOC	system organ class
SOT	solid organ transplant
SpO2	oxygen saturation
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
UPCR	urine protein to creatinine ratio
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P304, is based on the most recent approved clinical study protocol, including Amendment 4, dated 20-December-2021 and on the most recent approved electronic case report form (eCRF), dated 28-Feb-2022.

In addition to the information presented in the statistical analysis plan section of Protocol Amendment 4 (Section 8), which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P304 is a Phase 3b open-label study to evaluate the safety, reactogenicity, and immunogenicity of messenger ribonucleic acid (mRNA)-1273 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccine in adult solid organ transplant recipients and healthy controls.

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

In this document, subject, patient, and participant are used interchangeably; injection of investigational product (IP), dose, study vaccine, study IP, and study injection are used interchangeably; Booster injection, booster vaccine, booster dose (BD), and booster are used interchangeably.

2. Study Objectives

2.1. Primary Objective

The primary objectives for Part A are the following:

- To evaluate the safety of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens
- To evaluate the reactogenicity of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens
- To evaluate serum neutralizing antibody (nAb) responses to doses of 100 µg mRNA-1273 obtained 28 days after second or third dose

The primary objectives for Part B are the following:

- To evaluate the safety of the 100 µg BD of mRNA-1273
- To evaluate serum nAb responses elicited by the 100 µg mRNA-1273 obtained 28 days after the BD

2.2. Secondary Objectives

The secondary objectives for Part A are the following:

- 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
- 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
- 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
- To describe the incidence of coronavirus disease 2019 (COVID-19) after vaccination with mRNA-1273 in SOT recipients and healthy participants
- To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine
- To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine

2.3. Exploratory Objectives

The exploratory objectives for Part A are the following:

- To evaluate the genetic and/or phenotypic relationships of 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
- 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
- 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

- 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

The exploratory objectives for Part B are the following:

- 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
- 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
- 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
- To describe the incidence of COVID-19 after vaccination with mRNA-1273 in SOT recipients and healthy participants
- To describe changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine
- To describe changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine
- To evaluate the genetic and/or phenotypic relationships of 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
- 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
- To assess, in a subset of SOT recipients and healthy participants who received BD, SARS-CoV-2 S protein-specific T-cell responses
- 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

3. Study Endpoints

Generally, safety objectives are assessed through the evaluation of adverse events (AEs), laboratory test results, and vital signs measurements. Reactogenicity objectives are assessed through the evaluation of solicited local and systemic adverse reactions (ARs).

3.1. Primary Endpoints

The safety of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens will be evaluated by the following endpoints:

- Unsolicited 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

The reactogenicity of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens will be evaluated by the following endpoints:

- Solicited local and systemic 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 booster dose)

The nAb responses to doses of 100 µg mRNA-1273 obtained 28 days after the second dose or third dose will be evaluated by the following endpoints:

- The geometric mean concentration (GMC) of serum SARS-CoV-2-specific nAb after the second dose (Day 57 for unvaccinated participants)
- The GMC of SARS-CoV-2-specific nAb 28 days after dose 3 (Day 113 for unvaccinated SOT recipients and Day 29 for previously vaccinated SOT recipients)

The safety of 100 µg BD of mRNA-1273 will be evaluated by the following endpoints:

- 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

The reactogenicity of 100 µg BD of mRNA-1273 will be evaluated by the following endpoint:

- Solicited local and systemic ARs through 7 days after BD injection

The nAb responses to 100 µg BD of mRNA-1273 obtained 28 days after the BD will be evaluated by the following endpoints:

- The GMC of serum SARS-CoV-2-specific nAb28 days after the BD in SOT participants who received the Moderna primary series
- The GMC of SARS-CoV-2-specific nAb 28 days after BD in SOT participants who received mRNA or non-mRNA COVID-19 vaccine primary series outside the study

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

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 S-specific bAb through 1 year after dose 2 or dose 3 will be evaluated by the following endpoints:

- 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)
  - 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)
  - 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 with 2 doses of Moderna COVID-19 vaccine 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)

  - 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)
  - 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 with 2 doses of Moderna COVID-19 vaccine 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)

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 will be evaluated by the following endpoints:

- For all unvaccinated participants, the GMCs of SARS-CoV-2-specific nAb on Day 1 and Day 29 (28 days after dose 1)
  - For participants in the 2-dose regimen, GMC will be evaluated on Day 209 (6 months after dose 2) and Day 394 (1 year after dose 2)
  - For participants in the 3-dose regimen, GMC 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 with 2 doses of Moderna COVID-19 vaccine SOT recipients, GMCs 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)
  - 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).
  - 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 with 2 doses of Moderna COVID-19 vaccine 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).

3.2.2. Secondary COVID-19 and SARS-CoV-2 Infection Endpoints

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 will be evaluated by the following endpoints:

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) (central lab or local diagnostic tests) counted starting 14 days after the second and after the third dose of vaccine

The incidence of COVID-19 after vaccination with mRNA-1273 in SOT recipients and healthy participants will be evaluated by the following endpoints:

- 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:
  - 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

- 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
- Significant acute renal, hepatic, or neurologic dysfunction, OR
- 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.

3.2.3. Secondary Transplant Impact Endpoints

The changes in liver and renal function through laboratory tests over time in SOT recipients after vaccination with mRNA-1273 vaccine will be evaluated by the following endpoints:

- 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:
  - 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.
  - For previously vaccinated with 2 doses of Moderna COVID-19 vaccine SOT recipients, from Day 1 (dose 3) through Day 29 (28 days after dose 3).

The changes in immunosuppressant medications in SOT recipients after vaccination with mRNA-1273 vaccine will be evaluated by the following endpoints:

- 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, OR
  - Addition of new immunosuppressants, OR
  - Switching from 1 maintenance rejection prophylaxis regimen to another.

3.3. Exploratory Endpoints

The exploratory endpoints of 100 µg mRNA-1273 administered in 2-dose or 3-dose regimens are the following:

- Comparison of genetic sequence of viral isolates with that of the vaccine sequence
- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19
- 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
- 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
- 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

The exploratory endpoints of 100 µg BD of mRNA-1273 are the following:

- The GM value of SARS-CoV-2 S2P specific bAb on BD-Day 1, BD-Day 29 (28 days after BD), and BD-Day 181 (6 months after BD)
- The GM values of SARS-CoV-2-specific nAb on BD-Day 1, BD-Day 29 (28 days after BD), and BD-Day 181 (6 months after BD)

The incidence of asymptomatic SARS-CoV-2 infection after BD with mRNA-1273 vaccination in adult SOT recipients and healthy adult participants with negative SARS-CoV-2 at baseline will be evaluated by the following endpoints:

- 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 BD, OR
- Positive RT-PCR counted starting 14 days after the BD

The incidence of COVID-19 after BD with mRNA-1273 in SOT recipients and healthy participants will be evaluated by the following endpoints:

- First occurrence of COVID-19 starting 14 days after BD, 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 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, where severe COVID-19 is defined as symptomatic COVID-19 AND any of the following:
  - Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level, or PaO2/ FIO2 < 300 mm Hg, OR
  - ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation, or evidence of shock (systolic BP < 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 secondary case definition of COVID-19 is defined as the following symptoms:
  - Fever (temperature ≥ 38 °C) 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.

The changes in liver and renal function through laboratory tests over time in SOT recipients after BD with mRNA-1273 vaccine will be evaluated by the following endpoints:

- Safety laboratory assessments of kidney (serum creatinine, urine protein, and UPCR) and liver (ALT, AST, ALP, and bilirubin) function from BD-Day 1 through BD-Day 29 (28 days after BD):

The changes in immunosuppressant medications in SOT recipients after BD with mRNA-1273 vaccine will be evaluated by the following endpoints:

- Change in immunosuppressant medications to treat organ transplant rejection or to improve immune tolerance from BD-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, OR
  - Addition of new immunosuppressants, OR
  - Switching from 1 maintenance rejection prophylaxis regimen to another.

The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence will be evaluated by the following endpoints:

- Comparison of genetic sequence of viral isolates with that of the vaccine sequence

The clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection; and 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 after BD with mRNA-1273 vaccine will be evaluated by the following endpoints:

- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 or having COVID-19
- GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (IgG) and percent of study participants with 2×, 3×, and 4× rise of bAb relative to baseline

The SARS-CoV-2 S protein-specific T-cell responses and the epitopes recognized by B-cell and antibodies responses in a subset of SOT recipients and healthy participants who received BD will be evaluated by the following endpoints:

- Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells at BD-Day 1 and BD-Day 8
- Magnitude and phenotype of S protein specific B cells as measured by flow cytometry at BD-Day 1 and BD-Day 8
- Determination of targeted major antigenic sites and amino acid residues on SARS-CoV-2 S protein

4. Study Design

4.1. 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 at ~20 sites in US and non-US sites.

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 series vaccines with mRNA or non-mRNA COVID-19 vaccine under EUA outside the study will be enrolled in Part B (Group B4).

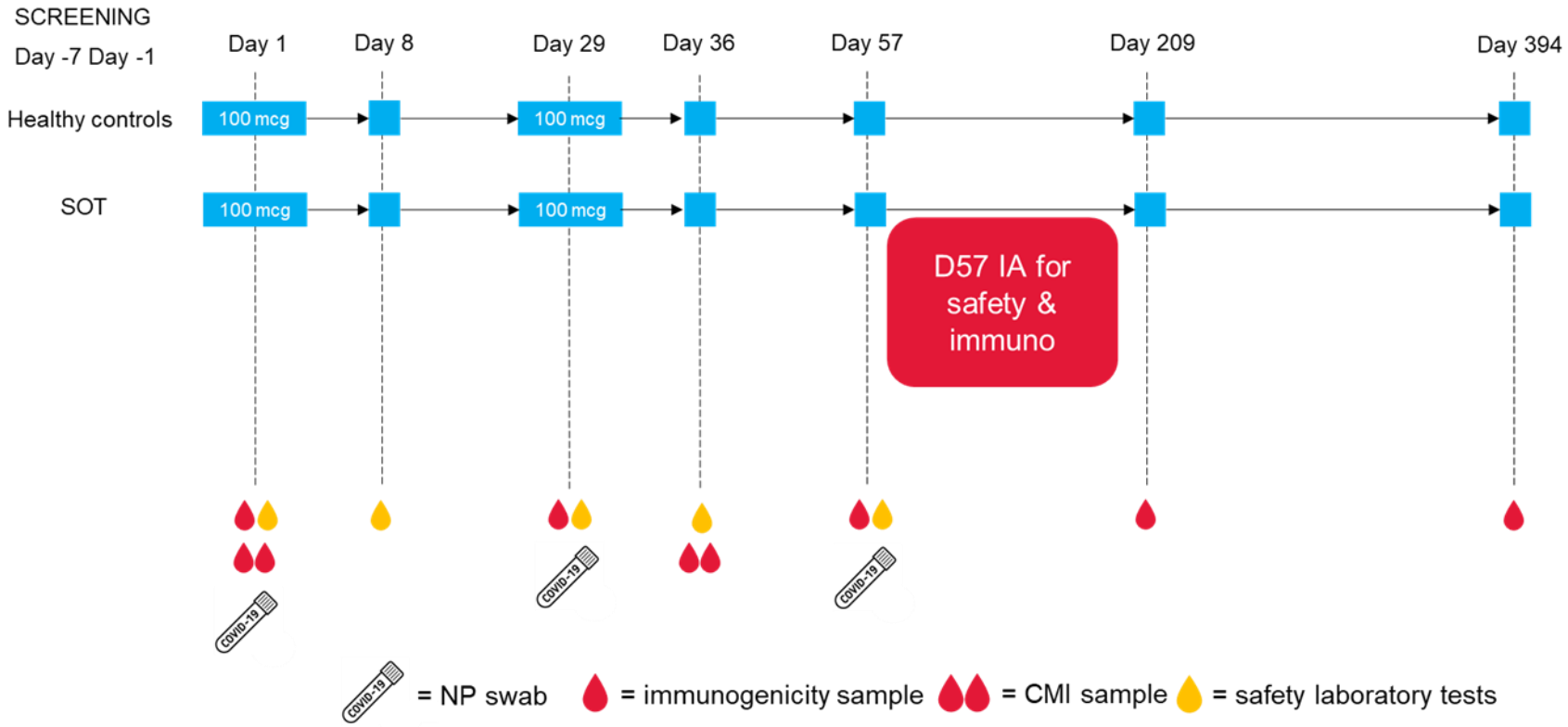
In Part A, all SOT recipients who were unvaccinated prior to enrollment will receive 2 doses of 100 µg of mRNA-1273 (vaccine) 28 days apart (window of -3/+7 days for the second dose) (Group A1). The SOT recipients will be offered the opportunity to receive a third dose of vaccine at Day 85 (window of -3/+7 days for the third dose) (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 (Group A2 to Group B2). 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 (Group A3 to Group B3). SOT participants who completed primary series vaccines with mRNA or non-mRNA COVID-19 vaccine outside of the study who consent to receive 1 booster dose in Part B (Group B4). Healthy participants who will be enrolled will be given 2 100 µg doses in Part A then proceed to Part B to receive a 100 µg booster dose (Group A5 to Group B5).

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.

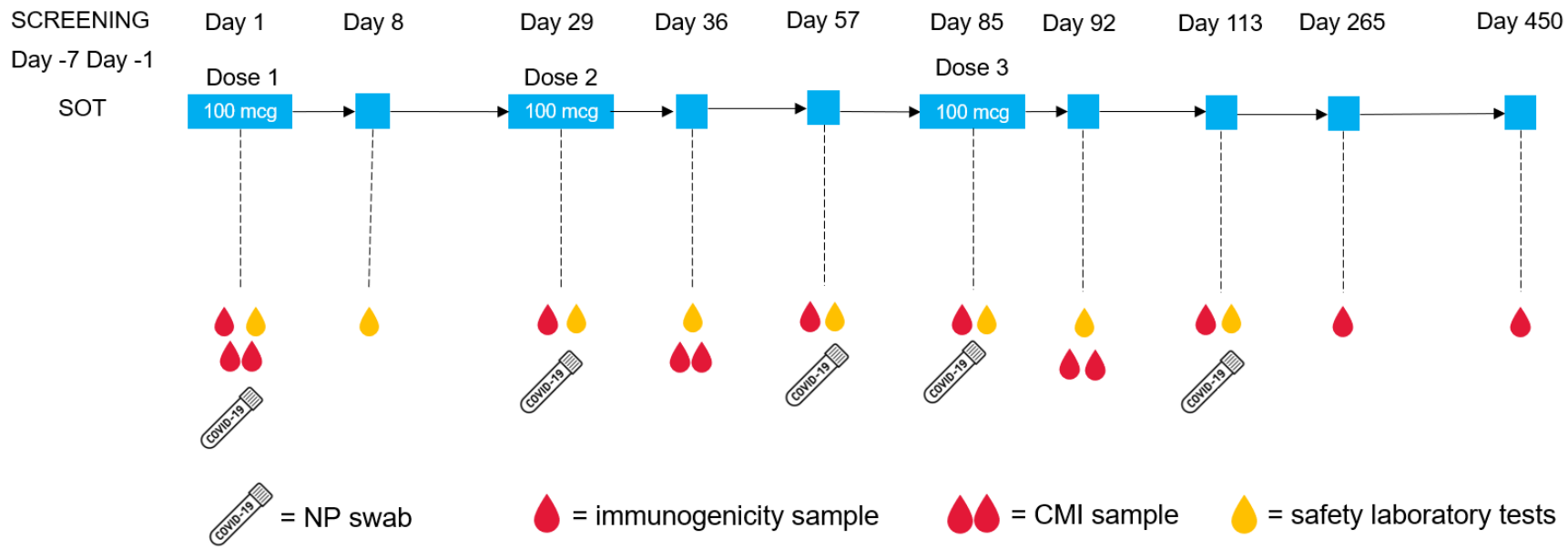
The schematic of study arms and major study events is illustrated in Figure 1, Figure 2, Figure 3, and Figure 4. The schedules of events for the study are presented in Section 10.1 of Protocol Amendment 4. Study arms and doses are presented in **Error! Reference source not found.** of Protocol Amendment 4.

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



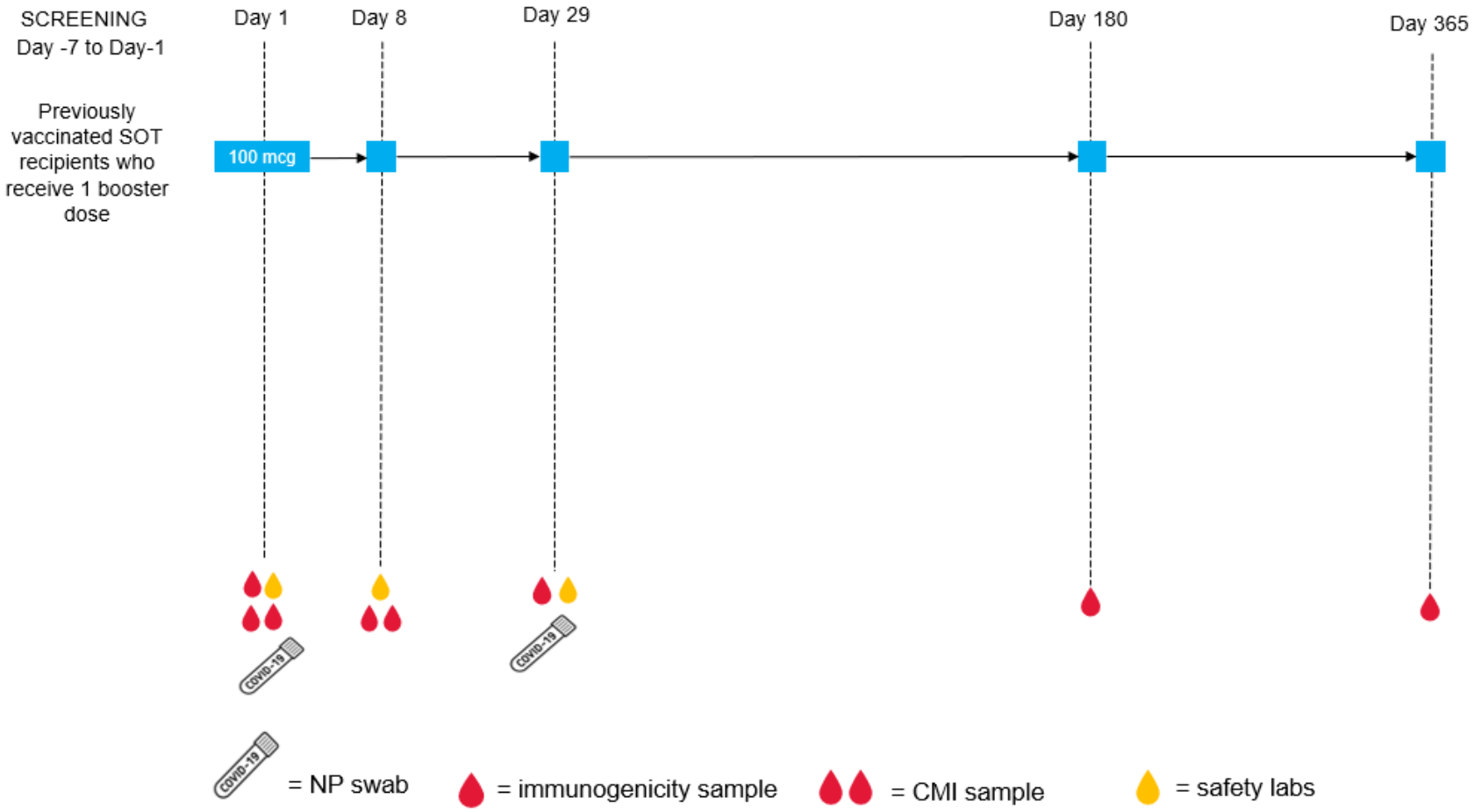
Abbreviations: CMI = cell-mediated immunity; IA = interim analysis; immuno = immunogenicity; NP = nasopharyngeal; SOT = solid organ transplant (recipients).

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



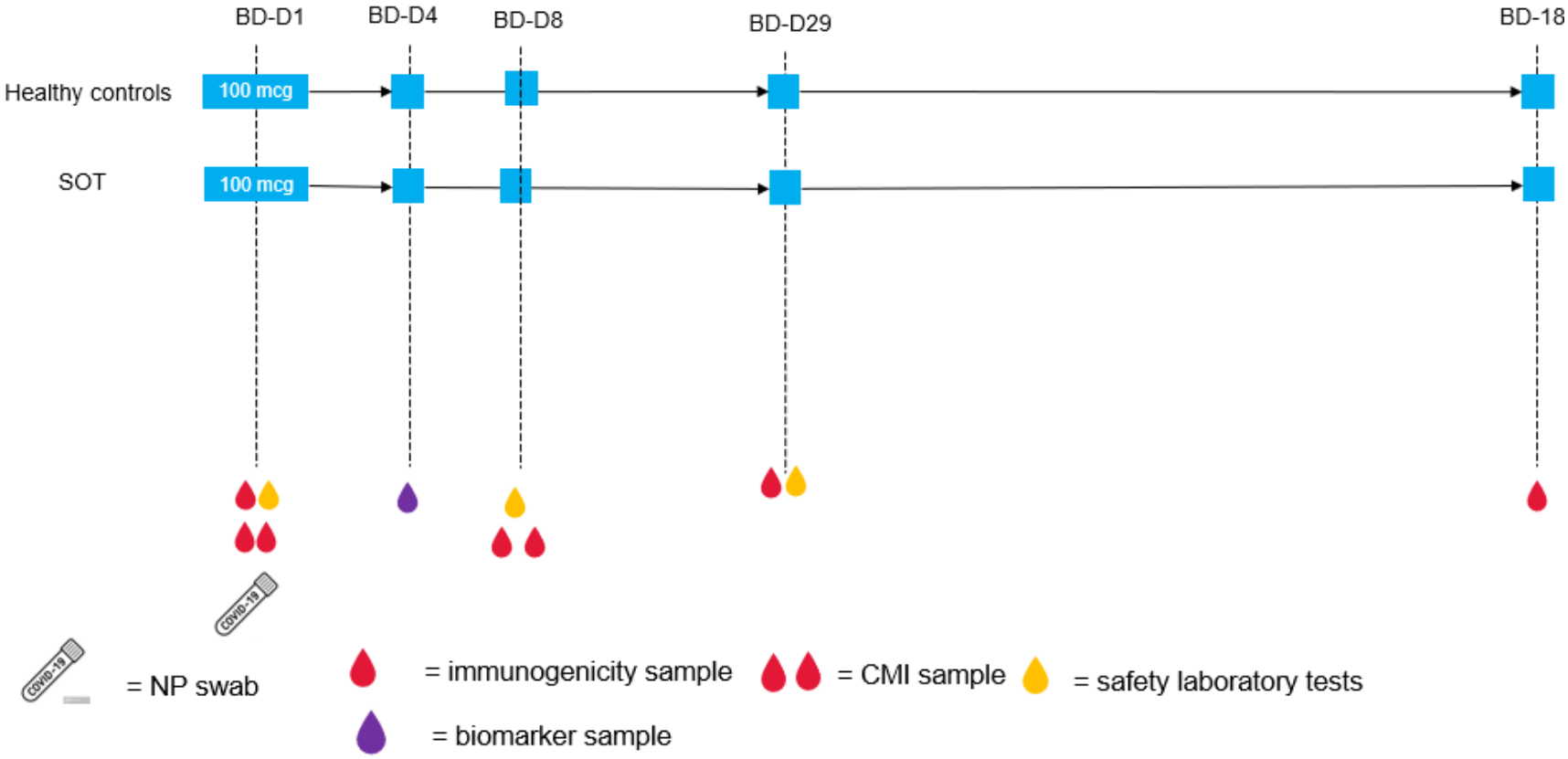
Abbreviations: CMI = cell-mediated immunity; NP = nasopharyngeal; SOT = solid organ transplant (recipients).

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. Study Schema for Booster Dose Phase (Part B)



4.2. Sample Size and Power

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 dose of mRNA-1273 vaccine among kidney and liver transplant recipients, is expected to provide clinical data to determine whether this cohort of immunocompromised participants has immune responses following vaccination 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 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-Day 29 for Part B 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.

4.3. Randomization

No randomization will be used in this study, as it is open-label and only a single intervention (100 µg mRNA-1273) is used for both primary series and BD.

4.4. Blinding and Unblinding

No blinding or unblinding will be performed as the study is open-label.

5. Analysis Populations

The following analysis sets are defined for Part A and Part B: Full Analysis/Safety Set, Modified Intent-to-Treat Set, Modified Intent-to-Treat-1 Set, Per-Protocol Set, Per-Protocol Immunogenicity Set, and Solicited Safety Set. Part A and Part B will share the same definition for Full Analysis/Safety Set and Solicited Safety Set.

5.1. Full Analysis/Safety Set

The Full Analysis/Safety Set consists of all participants who received at least one dose of IP in each part. SOT recipients who completed primary series vaccination with an mRNA or non-mRNA COVID-19 vaccine outside of the study will be included in the Full Analysis/Safety Set if received BD. The Safety Set is identical to the Full Analysis Set defined in the protocol. The Safety Set will be used for all analyses of safety except for the solicited ARs.

5.2. Analysis Population for Part A

All participants who are enrolled in Part A will be considered into analysis populations for Part A regardless of whether participants continue to Part B.

5.2.1. Modified Intent-to-Treat Set (Part A)

The Modified Intent-to-Treat (mITT) Set (Part A) includes all participants in Safety Set who had no immunologic or virologic evidence of prior COVID-19 (ie, negative RT-PCR test and bAb against SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) below limit of detection [LOD] or lower limit of quantification [LLOQ]) at baseline/pre-vaccination before the first dose of IP.

5.2.2. Per-Protocol Set (Part A)

The Per-Protocol (PP) Set (Part A) includes all participants in the mITT set (Part A) who received planned doses of study vaccination per schedule and had no major protocol deviations that impact key or critical data.

5.2.3. Per-Protocol Immunogenicity Set (Part A)

The PP Immunogenicity Set (Part A) includes all participants in the mITT Set (Part A) who received planned doses of study vaccination per schedule, complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective, and participant

had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective.

The PP Immunogenicity Set (Part A) will serve as the primary analysis population for the analysis of SARS-CoV-2-specific bAb and nAb immunogenicity data in Part A.

5.3. Analysis Populations for Part B

All participants who are enrolled in Part A and continues to Part B will be considered into analysis populations for Part B. SOT recipients who completed primary series vaccination with an mRNA or non-mRNA COVID-19 vaccine outside of the study who consent to receive BD in Part B will be included in Part B analysis populations.

5.3.1. Modified Intent-to-Treat Set (Part B)

The mITT Set (Part B) consists of all participants in the Safety Set who received BD and had no immunologic or virologic evidence of prior COVID-19 (ie, negative RT-PCR test and bAb against SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay)) below LOD or LLOQ at pre-booster before the BD.

5.3.2. Per-Protocol Set (Part B)

The PP Set (Part B) includes all participants in the mITT set (Part B) who received planned BD per schedule and had no major protocol deviations that impact critical or key data.

5.3.3. Per-Protocol Immunogenicity Set (Part B)

PP Immunogenicity Set (Part B) includes all participants in the mITT Set (Part B) who received planned BD per schedule, and SOT recipients who completed primary series vaccination with an mRNA or non-mRNA COVID-19 vaccine outside of the study that are in the mITT Set (Part B). The participants who complied with the timings of immunogenicity blood sampling to have post-booster results available for at least one assay component corresponding to the immunogenicity analysis objective, and participant had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective will be included.

The PP Immunogenicity Set (Part B) will serve as the primary analysis population for the analysis of SARS CoV 2-specific bAb and nAb immunogenicity data in Part B.

5.4. Solicited Safety Sets

The Solicited Safety Sets are considered relative to each (first, second, third, booster) injection, and consist of all participants who received the study injection (Safety Set) and contributed any solicited AR data following that injection. SOT recipients who completed primary series vaccination with an mRNA or non-mRNA COVID-19 vaccine outside of the study will be included in the Booster Injection Solicited Safety Set if received BD and contributed AR data following BD. The Solicited Safety Set will be used for the analyses of solicited ARs. The following Solicited Safety Sets are defined for each injection separately.

The **First Study Injection Solicited Safety Set** consists of all subjects in the Safety Set who have received the first study injection and have contributed any solicited AR data from the time of first study injection through the following 6 days.

The **Second Study Injection Solicited Safety Set** consists of all subjects in the Safety Set who have received a second study injection and have contributed any solicited AR data from the time of second study injection through the following 6 days.

The **Third Study Injection Solicited Safety Set** consists of all subjects in the Safety Set who have received a third study injection and have contributed any solicited AR data from the time of third study injection through the following 6 days.

The **Booster Injection Solicited Safety Set** consists of all subjects in the Safety Set who have received a BD and have contributed any solicited AR data from the time of BD through the following 6 days.

The **Any Study Injection Solicited Safety Set** is used to summarize certain endpoints after any injection and is the logical union of the First Injection Solicited Safety Set, and, when applicable, the Second Study Injection Solicited Safety Set, the Third Study Injection Solicited Safety Set, and the Booster Injection Solicited Safety Set.

6. Statistical Analysis

6.1. General Considerations

The schedule of assessments is provided in Appendix 1 of Protocol Amendment 4.

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

Categorical variables will be summarized using counts and percentages.

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

Pre-booster baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the BD on BD-Day 1.

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

When count data are presented, the percentage will not be displayed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the specified group within the analysis set of interest, unless otherwise specified.

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

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

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

Pre-booster SARS-CoV-2 status, is determined by using virologic and serologic evidence of SARS-CoV-2 infection prior to the BD in Part B.

Positive pre-booster SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before the date of BD (BD-Day 1).

Negative pre-booster SARS-CoV-2 status is defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster), i.e. RT-PCR result is not positive if available at BD-Day 1 and a negative bAb specific to SARS-CoV-2

nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before BD-Day 1.

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

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

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

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

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

b) Study day on or after the date of the first study injection but before the second study injection (if applicable) will be calculated as: date of assessment/event – date of the first study injection + 1;

c) Study day on or after the date of the second study injection but before the third study injection (if applicable) will be calculated as: date of assessment/event – date of the second study injection + 1;

d) Study day on or after the date of the second study injection will be calculated as: date of assessment/event – date of the second study injection + 1 provided that if study day is on the same day as the second study injection, the time is after the second study injection time;

e) Study day on or after the date of the third study injection but before the BD (if applicable) will be calculated as: date of assessment/event – date of the third study injection + 1;

f) Study day on or after the date of the third study injection will be calculated as: date of assessment/event – date of the third study injection + 1 provided that if study day is on the same day as the third study injection, the time is after the third study injection time;

g) Study day on or after the date of the BD will be calculated as: date of assessment/event – date of the BD + 1 provided that if study day is on the same day as the BD, the time is after the BD time.

For calculation regarding antibody levels/concentrations, antibody values reported as below LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be used as available. Values that are reported as greater than ULOQ (>ULOQ) without actual values will be replaced by ULOQ for analysis. Missing results will not be imputed, unless otherwise specified.

The following Analysis Stages will be defined for use in this study:

- Up to 28 days after any vaccination:

  This stage starts at the day of each vaccination and continues through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used as the primary analysis period for safety analyses (including unsolicited AEs), except for solicited ARs, unless specified otherwise.

- Throughout the study period:

  For subjects in Part A, this analysis period starts at the first study injection on Day 1 and continues through the earliest date of study completion (or prior to BD), discontinuation from the study, or death.

  For subjects in Part B, this analysis period starts at the BD on BD-Day 1 and continues through the earliest date of study completion, discontinuation from the study, or death.

  For subjects in Part A and Part B, this analysis period starts at the first study injection on Day 1 and continues through the earliest date of study completion, discontinuation from the study, or death.

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

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

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B. Results in previously vaccinated participants who received a third

injection in the study will be presented in tables, figures, and listings at study visits related to the third injection.

Incomplete/missing data will be handled by the following conventions**:**

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix C.
- For laboratory assessments, if the majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary.
- For immunogenicity assessments, imputation of missing results will be considered based on description in Section 6.4.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Participant groups will be summarized according to the schema below.

- Transplant status:
  - SOT Kidney
  - SOT Liver
  - SOT Total
  - 2-Dose Healthy
- Dosing regimens:
  - Overall
  - Unvaccinated SOTs Who Received 2 Doses
  - Unvaccinated SOTs Who Received 3 Doses
  - Previously Vaccinated SOTs Who Received a Third Dose
  - Total SOTs Who Received 3 Doses
  - Primary Series All SOTs Who Received a Booster Dose
- Primary Series All SOTs Who Received a Booster Dose:
  - Overall
  - 3-Dose Moderna
  - 3-Dose Pfizer

- Other

Unless otherwise mentioned, the results of the analyses will be summarized according to the participant groups above. Subjects under the same dosing regimen may be combined for analyses regardless of BD. Participants that received booster may be analyzed separately from participants that did not receive booster.

Subgroup analyses for safety and immunogenicity endpoints may be analyzed in select subgroups specified below as applicable:

- Age (18 to < 65, ≥ 65)
- Time of post-transplantation (< 2, ≥ 2 years)
- Baseline SARS-CoV-2 Status in each part (Positive, Negative) (for safety data)
- Sex (Male, Female)
- Race (White, Communities of color)
- Anti-metabolite immunosuppression (Yes, No)
- Combination of immunosuppressants (Mycophenolate, Tacrolimus, and Prednisone; Mycophenolate and Tacrolimus; Tacrolimus; and Other)
- Previous induction therapy (Basiliximab or other monoclonal antibody; Basiliximab or other monoclonal antibody with steroids; Thymoglobulin; Thymoglobulin with steroids; or steroids alone)

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

6.2. Background Characteristics

Participant background characteristics will be presented by participant group for the Safety Set, unless otherwise stated.

6.2.1. Subject Disposition

The number and percentage of subjects in the following analysis populations will be summarized by participant group as defined in Section 6.1 based on the Safety Set:

- Full Analysis/Safety Set
- mITT (Part A/Part B)

- PP Set (Part A/Part B)
- PP Immunogenicity Set (Part A/Part B)
- Solicited Safety Set

Percentages displayed will be based on the number of subjects within each participant group.

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

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

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

The number and percentage of subjects in each of the following disposition categories will be summarized by participant group based on the Safety Set:

- Enrolled into the study by site
- Received each dose of IP
- Prematurely discontinued before receiving the second or third dose of IP and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

A subject disposition listing will be provided, including informed consent, subjects who completed the study injection schedule, subjects who completed study, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

A subject who did not receive BD and completed 12 months of follow up after the last injection received is considered to have completed the study. A subject who consented to receive BD and completed 6 months of follow up after the BD is considered to have completed the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2), and previous vaccination history. Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity. The summaries will be presented by participant group as defined in Section 6.1. based on the Safety Set, mITT Set (Part A/Part B), and the PP Immunogenicity Set (Part A/Part B).

For screened failure subjects, age (years), as well as gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Transplant characteristics

Baseline transplant characteristics, including type of transplant, time since transplant (months), type of donor transplant, indication for transplant, ABO blood group status, and relevant medical history will be summarized for transplant recipients by participant group and presented in a listing.

Relevant medical history for SOT recipients includes history of human leukocyte antigen mismatch, induction therapy, panel reactive antibodies, and prior transplant rejection.

6.2.4. Medical History

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

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

Medical history data will be presented in a listing.

6.2.5. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). Summaries of concomitant medications will be based on the Safety Set. Prior medications are defined as those reported medications that are taken prior to the first study injection. For SOT participants, prior immunosuppressants received within 3 months prior to the first study injection will be included. Concomitant medications are defined as those medications that are taken from the time of any injection through the following 28 days following the injection. In this manner, a medication can be both prior and concomitant. For SOT participants, concomitant immunosuppressant medications, including but not limited to, glucocorticoids, immunophilin binding agents, and inhibitors of de novo nucleotide synthesis within 28 days prior to the first study injection and throughout the study, and any immunosuppressants listed in the exclusion criteria if taken during the study will be included. The handling of missing or partial start and end dates for medications is described in Appendix C. The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by participant group as defined in Section 6.1 and as follows:

- Any concomitant medications and non-study vaccination within 7 days post-injection
- Any concomitant medications and non-study vaccination within 28 days post-injection
- Seasonal influenza vaccine within 28 days post-injection
- Antipyretic or analgesic medication within 28 days post-injection

Medications taken to prevent pain or fever will be collected on eDiary and summaries will be provided based on each of the Solicited Safety Sets by participant group as defined in Section 6.1 for each injection (first, second, third, or BD) and for any injection.

A separate summary table of the number and percentage of subjects using concomitant immunosuppressive medications will be summarized by participant group and presented by PT. In addition, a summary table will be provided for the number and percentage of subjects who experienced any change in immunosuppressant therapy from Day 1 through

the end of the study by participant group. Immunosuppressive medications, including any change in immunosuppressant therapy, the description of this change, and the reason for this change will be presented in a separate listing.

Prior and concomitant medications and non-study vaccinations will be presented in a listing.

Concomitant procedures will be presented in a listing.

6.2.6. Study Exposure

Study IP administration data will be presented in a listing.

Study duration will be summarized since date of the first/second/third study injection, since the date of the BD, and date from the last injection in Part A to BD.

6.2.7. Major Protocol Deviations

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

The number and percentage of the subjects with each major protocol deviation type will be provided by participant group as defined in Section 6.1 based all enrolled subjects.

Major protocol deviations will be presented in a listing.

6.2.8. COVID-19 Impact

A listing will be provided for the impact of COVID-19 on the execution of the study.

6.3. Safety and Reactogenicity Analysis

Safety will be assessed by clinical review of all relevant parameters including solicited ARs, unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal from study vaccine and/or study participation, vital signs, and physical examination findings.

Reactogenicity will be assessed by clinical review of solicited ARs (local and systemic).

6.3.1. Adverse Events

Unsolicited AEs are collected for the purpose of assessing safety. All safety analyses will be based on the Safety Set.

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

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

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by participant group and analysis stage (up to 28 days after any vaccination and throughout the study period from Day 1 (Part A)/BD-Day 1 (Part B)/Day 1 (Part A and Part B); see Section 6.1 for definitions of participant group and analysis stage).

Similarly, adverse events related to organ rejection status will be reviewed by an adjudication committee as described in Section 7.6.1 of Protocol Amendment 4 to determine whether they represent an adjudicated biopsy-proven organ rejection. Events that are adjudicated as biopsy-proven organ rejection will be summarized for transplant recipients by participant group and analysis stage Adjudication results will be listed.

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

Percentages will be based upon the number of subjects in the Safety Set within each participant group.

6.3.1.1. Incidence of Adverse Events

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

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any TEAEs adjudicated as biopsy-proven organ rejection
- Any unsolicited medically-attended TEAEs
- Any Grade 3 or higher ARs or TEAEs
- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs

The table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related in each of the above categories. This table will also be presented by the subgroups named in Section 6.1.

In addition, listings containing individual subject AE data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, unsolicited medically-attended AEs, and TEAEs adjudicated as biopsy-proven organ rejection will be provided, separately.

6.3.1.2.TEAEs by System Organ Class and Preferred Term

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

- All unsolicited TEAEs
- All unsolicited TEAEs by the subgroups named in Section 6.1
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study

- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related
- All TEAEs adjudicated as biopsy-proven organ rejection
- All TEAEs that are AESI

6.3.1.3. TEAEs by Preferred Term

A summary table of all unsolicited TEAEs by PT only will be provided. PTs will be sorted in a descending order according to the overall frequency.

6.3.1.4. TEAEs by System Organ Class, Preferred Term and Severity (or Grade)

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

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

6.3.2. Solicited Adverse Reactions

Solicited ARs are collected for the purpose of assessing reactogenicity. All listings and summaries of solicited ARs will be based on the Solicited Safety Set.

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs).

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

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

The solicited ARs will be graded based on the grading scales presented in Table 3 in Protocol Amendment 4, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). The investigator will assess Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post-injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution.

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

Analyses of solicited ARs will be provided by participant group for each injection (first, second, third, or BD) based on the associated subset of Solicited Safety Set, i.e. First, Second, Third Study Injection Solicited Safety Set, or Booster Injection Solicited Safety Set; and for any injection based on the Any Study Injection Solicited Safety Set, unless otherwise specified.

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

The number and percentage of subjects who reported each individual solicited AR will also be summarized by participant group, severity grade, and day of reporting.

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

The onset of individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by participant group and study day relative to the corresponding injection (Day 1 through Day 7).

The number and percentage of participants experiencing solicited ARs persisting beyond 7 days after each injection will be summarized.

The number of days reporting each solicited AR will be summarized descriptively. The number of days will be calculated as the days of the solicited AR is reported within the 7 days of injection including the day of injection, no matter if it is intermittent or continued. If the solicited AR continues beyond 7 days, the days a solicited AR is reported after 7 days will be included (e.g., in the case of an event that lasted 5 days in the first 7 days post-injection and 3 days beyond 7 days post-injection, the duration will be reported as 8 (5 + 3) days). In addition, the duration for each solicited AR that started within 7 days of injection will be summarized descriptively. The duration of the solicited AR will be calculated as the last day – the first day + 1.
Solicited ARs occurring within 7 days following the first, second, third study injection will be presented by the subgroups described in Section 6.1. Likewise, solicited ARs occurring within 7 days following the BD will also be presented in this manner.
Solicited ARs will be listed for the Safety Set/ Solicited Safety Set.

6.3.3. Clinical Laboratory Results

Clinical laboratory samples will be collected at the Day 1 visit and at post-baseline visits through the Day 57 visit for participants receiving 2 doses of IP, or through Day 113 visit for participants receiving 3 doses of IP, or through Day 29 visit for SOT participants that are previously vaccinated with Moderna COVID-19 vaccines. For participants that continue to Part B of the study and receive BD, clinical laboratory samples will be collected at BD-Day 1, BD-Day 8, and BD-Day 29. Results will be summarized using descriptive statistics at each visit by participant group and will be presented in a data listing for the Safety Set.

Using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007), as described in Table 5, the number and percentage of participants experiencing clinical laboratory abnormalities and changes from baseline values at each visit will be summarized by severity grade and participant group. Similarly, clinical laboratory toxicity will be summarized as the maximum over all post-injection visits. Clinical laboratory results and their toxicity grades will also be listed for the Safety Set.

6.3.4. Pregnancy Tests

A point-of-care urine pregnancy test will be performed at the Screening Visit and before each dose, including BD. In addition, at the discretion of the investigator, a pregnancy test

either via blood or point-of-care urine test can be performed at any time. A listing of all pregnancy tests for participants with positive pregnancy tests will be provided.

6.3.5. Vital Sign Measurements

Vital signs will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). This grading scale is displayed in Table 6.

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, and baseline height, weight, and BMI will be presented in a data listing.

The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 2 or higher abnormality at any post-injection visit, then all results of vital sign measurement for that subject will be presented in the listing. The abnormal values meeting the toxicity grading criteria will be flagged in the data listing.

Observed values and changes from baseline for all vital sign measurements will be summarized at each visit by participant group as defined in Section 6.1. Shift from baseline in the toxicity grades at each visit (including post-dose assessment on day of injection) and shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized by participant group. Change from baseline results and shift from baseline in toxicity grades will be based on pre-booster baseline (collected prior to BD on BD-Day 1) for participants in Part B.

6.4. Immunogenicity Analysis

Immunogenicity samples will be collected at baseline and post-baseline visits, as described in the Schedule of Events in Appendix 1 of Protocol Amendment 4. The PP Immunogenicity Set (Part A/Part B) is the primary analysis population used in the immunogenicity analyses, unless otherwise specified. The mITT set (Part A/Part B) will be used for sensitivity analyses. Concomitant medications and/or vaccines received during the study as described in Section 5.5.3 in Protocol Amendment 4 and Protocol Clarification Memorandum 11 as well as antiretroviral treatments that impact neutralizing antibody responses may be used to determine subject's immunogenicity samples that are eligible for the immunogenicity analyses. Participants will be summarized according to participant group as defined in Section 6.1.

The GM levels will be calculated using the following formula:

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

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

The GMFR measures the changes in immunogenicity levels within subjects. The GMFR will be calculated using the following formula:

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

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

6.4.1. Immunogenicity Assessments

The protocol mentions two types of immunogenicity assessments:

- 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.

In practice, Ab levels are measured using a variety of assays/tests. A complete list of these assays can be found in Appendix G. All summaries of Ab results will be performed by assay/test and participant group, unless otherwise specified.

Unless otherwise specified, summaries of immunogenicity described in this section will display 95% CIs, which are calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. Similarly, summaries will report the following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum, and maximum. Box plots and reverse cumulative distribution curves for each of these reported antibody assay/test results for at all scheduled time points will be presented.

6.4.2. Primary Analysis of Neutralizing Antibody Response

GMC of SARS-CoV-2-specific nAb with corresponding 95% CI will be provided at each time point. The GMC at Day 57 from unvaccinated participants in the 2-dose regimen, the GMC at Day 113 from unvaccinated participants in the 3-dose regimen, Day 29 for SOT participants that are previously vaccinated with Moderna COVID-19 vaccines, and BD-Day 29 for SOT participants that are previously vaccinated with Moderna COVID-19 vaccine/non-Moderna COVID-19 vaccine forms the basis for the evaluation of the primary immunogenicity objective. The GMC at other visits will help address the evaluation of the secondary immunogenicity objective related to nAb levels.

6.4.3. Secondary Analysis of Antibody-Mediated Immunogenicity Response

For each participant group, the following evaluations will be performed at each time point at which blood samples are collected for immunogenicity, unless otherwise specified.

For each of the reported assay/test results, the following analyses will be performed for both Part A and Part B, unless otherwise specified:

- GM levels of SARS-CoV-2-specific bAb or nAb with corresponding 95% CI will be provided at each time point.
- GMFR of SARS-CoV-2-specific bAb or nAb with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1.

  Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2 specific antibody levels from baseline at each post-baseline time points will be summarized with 2-sided 95% Clopper Pearson CIs.

6.4.3.1. Seroresponse Rate (SRR) of the Primary Series and Booster

For a subset of the antibodies of interest, seroresponse rate, defined as number of subjects achieving seroresponse, will be summarized at each post-baseline timepoint. There will be 2 baseline definitions used for determining seroresponse rate: 1) Pre-vaccination baseline is defined as the sample collected prior to any injection in Part A (primary series) and 2) Pre-booster baseline is defined as the sample collected prior to BD in Part B. Subjects that are enrolled in both Part A and Part B will be analyzed based on both types of baseline (pre-vaccination and pre-booster).

If missing pre-vaccination baseline (no available serum samples), and the subject did not have SARS-CoV-2 infection prior to vaccination (i.e. negative SARS-CoV-2 status at pre-vaccination of primary series), the subject's pre-vaccination baseline antibodies will be

assumed to be < LLOQ. Similarly, for SOT recipients who completed primary series vaccination with an mRNA or non-mRNA COVID-19 vaccine outside of the study, if pre-booster baseline antibodies are missing and the subject did not have SARS-CoV-2 infection prior to receiving BD (i.e. negative SARS-CoV-2 status), the subject's pre-booster baseline antibodies will be assumed to be < LLOQ.

- Two definitions for seroresponse will be used for analyses: 1) 4-fold rise seroresponse based on pre-vaccination baseline and 2) 4-fold rise seroresponse based on pre-booster baseline. Seroresponse based on pre-vaccination baseline is defined in 2 ways:
    - 4-fold rise seroresponse (primary approach), measured by an increase of SARS-CoV-2 specific bAb or nAb from pre-vaccination baseline < LLOQ to at least 4 x LLOQ, or a 4-fold or greater rise if pre-vaccination baseline ≥ LLOQ.
    - If assay-specific critical fold rise becomes available, seroresponse based on assay-specific critical threshold may be provided.
- The 4-fold rise definition will be used for seroresponse analyses at each post-baseline for all subjects in Part A (regardless of whether subjects continue to Part B) and all subjects in Part B.
- Seroresponse based on pre-booster baseline follows the same definition as pre-vaccination seroresponse.
- Difference in seroresponse rates between the BD and the primary series and among participant groups may be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method.

6.4.4. Exploratory Analysis of Antibody Responses Meeting Protection Threshold

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from the P301 study, an additional exploratory analysis will be performed by measuring the proportion of participants with a serum Ab level greater than or equal to the threshold at Day 57 for unvaccinated participants in the 2-dose regimen, at Day 113 for unvaccinated participants in the 3-dose regimen, and at Day 29 for previously vaccinated SOT participants in Part A. Exploratory analysis will be performed at BD-Day 29 and BD-Day 181 for participants who received BD in Part B. A 2-sided 95% CI using the Clopper-Pearson method by participant group will also be calculated. If an accepted serum Ab

threshold of protection against COVID-19 is not available, this summary will not be performed.

6.5. COVID-19 and SARS-CoV-2 Infection Analysis

For both Part A and Part B, the mITT Set (Part A/Part B) will be used for the analysis of COVID-19 and SARS-CoV-2 infection starting from 14 days after the second dose and third dose received for each participant group. The PP Set (Part A/Part B) may be used in the analyses as appropriate, unless otherwise specified.

Baseline SARS-CoV-2 status and Pre-booster SARS-CoV-2 Status is described in Section 6.1. The serology test results based on Roche Elecsys assay at baseline, and the RT-PCR test results at baseline will be summarized by participant group.

Participants with pre-vaccination baseline positive or missing SARS-CoV-2 status will be excluded from the mITT Set (Part A) infection analysis.

Participants with pre-booster positive or missing SARS-CoV-2 status will be excluded from the mITT Set (Part B) infection analysis.

The post-baseline serology test results based on the Roche Elecsys assay and the RT-PCR test results will also be summarized by visit.

6.5.1. Endpoint Definitions/Derivations

6.5.1.1. SARS-CoV-2 Infection

This is a combination of COVID-19 (defined in Section 6.5.1.3) and asymptomatic SARS-CoV-2 infection (defined in Section 6.5.1.2) for participants with negative SARS-CoV-2 status at baseline. The incidence of SARS-CoV-2 infection counted starting 14 days after the second dose, the third dose, and the BD of IP will be summarized by participant group. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline meeting the criteria below:

- 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 (at Day 57); 28 days after the third dose (at Day 113); and 28 days after the BD (BD-Day 28) or later, OR
- Positive RT-PCR counted starting 14 days after the second dose, third dose, and BD of IP

During the analysis, documented infection is counted starting 14 days after the second, third dose, and BD of IP, which requires positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid 28 days after the second, third dose, and BD, or a positive RT-PCR result starting 14 days after the second, third dose, and BD of IP. Derivation of this endpoint is summarized in Table 1 below.

Table 1. Derivation for SARS-CoV-2 Infection

	Post-baseline assessments		
Baseline SARS-CoV-2 Status	RT-PCR test post-baseline	bAb levels against SARS-CoV-2 Nucleocapsid	**Endpoint**: SARS-CoV-2 infection
Negative at Baseline of each part	**Positive** (either at scheduled NP swab test, or at symptom-prompt NP swab test 14 days after the second/third dose)		Case
Negative at Baseline of each part		**Positive** (28 days after the second, third dose, and BD or later) as measured by Roche Elecsys	Case

The date of documented infection will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of positive post-baseline serology test result based on bAb specific to SARS-CoV-2 nucleocapsid

For Part A, the time to the first documented SARS-CoV-2 infection will be calculated as:

Time to the first SARS-CoV-2 infection = Date of the first infection – Date of first study dose + 1.

For Part B, the time to the first documented SARS-CoV-2 infection will be calculated as:

Time to the first SARS-CoV-2 infection = Date of the first infection – Date of BD + 1.

Cases will be counted starting 14 days after the second, third dose, and BD, e.g., date of documented infection - Date of the second/third dose/BD $\geq$ 14.

6.5.1.2. Asymptomatic SARS-CoV-2 Infection

This is a secondary endpoint for Part A and exploratory endpoint for Part B. It is defined in participants with negative SARS-CoV-2 at baseline. Asymptomatic SARS-CoV-2 infection is identified by both the absence of symptoms and the presence of infection as detected by RT-PCR or serology tests. Specifically:

- Absent of COVID-19 symptoms within 14 days of positive virologic or serologic results
- AND at least one from below:
  - Positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid at scheduled visits, when blood samples for immunogenicity are collected, or
  - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits)

The date of documented asymptomatic SARS-CoV-2 infection is the earlier date of:

- Date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid, or
- Date of positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits), with absence of symptoms.

For Part A, the time to the documented asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection – Date of first study dose + 1.

For Part B, the time to the documented asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection – Date of BD + 1. Cases will be counted starting 14 days after the second dose and after the third dose, e.g., date of documented infection - Date of the second/third dose/BD $\geq$ 14.

6.5.1.3.COVID-19

The incidence of the first occurrence of COVID-19 starting 14 days after the second, third dose, and BD of IP will be presented. COVID-19 is defined as symptomatic disease based on the criteria specified in Section 3.2.2. Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results.

Surveillance for COVID-19 symptoms will be conducted every two weeks by either telephone calls or eDiary prompts (alternating). Subjects reporting COVID-19 symptoms, as defined in Section 7.3.2 of Protocol Amendment 4, will be arranged an illness visit to collect an NP swab.

For this endpoint, a COVID-19 case will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms as described below in Table 2.

Table 2. Derivation for COVID-19

	COVID-19
Post-baseline PCR results	Positive, **AND**
Systemic symptoms	at least **TWO** of the following **systemic symptoms**: Fever (≥ 38ºC/≥ 100.4º F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); **OR**
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.

The date of documented COVID-19 (case) will be the later date of ([2 systemic symptoms reported, or respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented COVID-19 will be the later date of the following two dates (date of

positive PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other. Specifically:

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

For Part A, the time to the first occurrence of COVID-19 will be calculated as:

Time to the first occurrence of COVID-19 = Date of documented COVID-19 – Date of first study dose + 1.

For Part B, the time to the first documented SARS-CoV-2 infection will be calculated as:

Time to the first occurrence of COVID-19 = Date of documented COVID-19 – Date of BD + 1.

Cases will be counted starting 14 days after the second dose, third dose, and BD, e.g., date of documented COVID-19 - Date of the second/third dose/BD ≥ 14.

Table 3 includes the days when a RT-PCR test is scheduled for each of the 2-dose and the 3-dose regimens with/without booster. For the analysis of this endpoint, RT-PCR results at scheduled pre-dose visits will not be considered in the derivation of COVID-19 cases.

6.5.1.4. Severe COVID-19

The incidence of the first severe COVID-19 starting 14 days after the second dose and after the third dose of IP. Severe COVID-19 is defined as COVID-19 (as defined above in Section 6.5.1.3) in conjunction with any of the following:

- 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
- Respiratory failure or ARDS, defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation) or 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

For Part A, the time to the first occurrence of severe COVID-19 will be calculated as:

Time to the first occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of first study dose + 1.

For Part B, the time to the first documented SARS-CoV-2 infection will be calculated as:

Time to the first occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of BD + 1.

Cases will be counted starting 14 days after the second dose, third dose, and BD, e.g., date of documented Severe COVID-19 – Date of second/third dose/BD ≥ 14.

6.5.1.5. Secondary Case Definition of COVID-19

The incidence of the first secondary COVID-19 starting 14 days after the second dose and after the third dose of IP. The secondary case definition of COVID-19 is defined as one of these following systemic 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.

For Part A, the time to the first occurrence of secondary COVID-19 will be calculated as:

The time to the first occurrence of secondary COVID-19 = Date of documented secondary COVID-19 – Date of first study dose + 1.

For Part B, the time to the first occurrence of secondary COVID-19 will be calculated as:

The time to the first occurrence of secondary COVID-19 = Date of documented secondary COVID-19 – Date of BD + 1.

Cases will be counted starting 14 days after the second dose, third dose, and BD, e.g., date of documented secondary COVID-19 – Date of second/third dose/BD ≥ 14.

6.5.2. Analysis of Infection Rates

For Part A and Part B, the number and percentage of subjects experiencing each of the infection events below will be summarized by participant group for the mITT Set:

- SARS-CoV-2 infection
- Asymptomatic SARS-CoV-2
- COVID-19
- Severe COVID-19
- Secondary case definition of COVID-19

For each of these summaries, the incidence rate (i.e. the infection rate) will be provided by participant group, calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Person-time is defined as the total time from first dose of each part of the study (Part A or Part B) to the earliest of the following dates: date of event, dose date in next part, last date of study participation, censoring time, or efficacy data cutoff date.

For participants who are a case for symptomatic COVID-19, symptoms reported by these participants will be summarized.

For SARS-CoV-2 infection, asymptomatic SARS-CoV-2 infection, COVID-19, and severe COVID-19, the timeframe for the counting cases will begin at 14 days after the last planned dose and will differ by study arm:

- 2-dose unvaccinated without booster: from day 43 up to and including day 394,
- 3-dose unvaccinated without booster: from day 99 up to and including day 450,
- 3-dose previously vaccinated with Moderna COVID-19 vaccine without booster: from day 15 up to and including day 365.
- 2-dose unvaccinated with booster: from BD-Day 1 + 14 up to and including BD-Day 181.

- 3-dose unvaccinated with booster: from BD-Day 1 + 14 up to and including BD-Day 181)
- 3-dose previously vaccinated with Moderna COVID-19 vaccine with booster: from BD-Day 1+ 14 up to and including BD-Day 181.
- 3-dose previously vaccinated with mRNA or non-mRNA COVID-19 vaccine with booster: from BD-Day 1 + 14 up to and including BD-Day 181.

In addition, the COVID-19 and SARS-CoV-2 infection endpoints may be also analyzed by specimen types (i.e. NP swab, nasal swab, or saliva samples), calendar months, time periods, and all types of the diagnostic test (i.e., both RT-PCR results and other COVID-19 test results). The number and percentage of subjects experiencing COVID-19 may be summarized by specific variant groups. Listings of serum nAb and bAb levels against SARS-CoV-2, solicited ARs and unsolicited AEs will be provided for subjects infected by SARS-CoV-2.

6.6. Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed for Part A and B:

- The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.
- Descriptive summaries of GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline)
- The magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells will be summarized at each timepoint by participant group.
- The magnitude and phenotype of S protein-specific B cells relative to baseline will be summarized at each timepoint by participant group.
- Summaries of B-cell receptor sequence analysis to identify representative B-cell clones and determine major antigenic sites & amino acid residues on the SARS-CoV-2 S protein.

6.7. Interim Analysis

An interim analysis of safety and immunogenicity data is planned after Day 57 (28 days after the second study dose for unvaccinated participants) in Part A, after Day 29 (28 days after dose 3 in previously vaccinated SOT recipients) in Part A, and at BD-Day 29 (28 days after BD in participants who receive a BD) in Part B; a clinical study report will be prepared.

6.8. Data Safety Monitoring Board

No Data Safety Monitoring Board is used for this study. A Safety Review Committee (SRC), composed of a transplant nephrologist and hepatologist who are not involved in the conduct of the study, will monitor and adjudicate individual events of transplant rejection. This SRC is described in Section 7.6.1 of Protocol Amendment 4.

7. Changes from Planned Analyses in Protocol

Not applicable.

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2019 Apr 10] [10 screens].

Available from:
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.List of Appendices

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2019 Apr 10] [10 screens]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

9. List of Appendices

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

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

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

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

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

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

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 3 below.

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

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

Table 3. Visit Windows

	Visit Day (Month) [1]	Study Injection [2]	Visit Window by Regimen without Booster (Part A)		
			2-Dose Unvaccinated	3-Dose Unvaccinated	3-Dose Previously Vaccinated with Moderna COVID-19 Vaccine [3]
NP Swab for SARS-CoV-2 Safety Lab	1	First	≤1, Pre-dose	≤1, Pre-dose	
	29 (1)	Second	[2, 43]	[2, 43]	
	57 (2)		≥44	[44, 71]	
	85 (3)	Third		[72, 99]	≤1, Pre-dose
	113 (4)			≥100	≥2
	1	First	≤1, Pre-dose	≤1, Pre-dose	
	8		[2, 18]	[2, 18]	
	29 (1)	Second	[19, 32]	[19, 32]	
	36		[33, 46]	[33, 46]	
	57 (2)		≥47	[47, 71]	
	85 (3)	Third		[72, 88]	≤1, Pre-dose
	92			[89, 101]	[2, 18]
	113 (4)			≥102	≥19
Vital Signs	1	First	≤1, Pre-dose	≤1, Pre-dose	
	1	First	1, Post-dose	1, Post-dose	
	29 (1)	Second	[2, 29 Pre-dose]	[2, 29 Pre-dose]	
	29 (1)	Second	[29 Post-dose, 43]	[29 Post-dose, 43]	
	57 (2)		[44, 133]	[44, 71]	
	85 (3)	Third		[72, 85 Pre-dose]	≤1, Pre-dose
	85 (3)	Third		[85 Post-dose, 99]	1, Post-dose
	113 (4)			[100, 189]	[2, 104]
	180 (6)				
	209 (7)		[134, 301]		
	265 (9)			[190, 357]	[105, 272]
	365 (12)				
	394 (13)		≥302		

	450 (15)			≥358	≥273
Immunogenicity	1	First	≤1, Pre-dose	≤1 Pre-dose	
	29 (1)	Second	[2, 43]	[2, 43]	
	57 (2)		[44, 133]	[44, 71]	
	85 (3)	Third		[72, 99]	≤1, Pre-dose
	113 (4)			[100, 189]	[2, 104]
	180 (6)				
	209 (7)		[134, 301]		
	265 (9)			[190, 357]	[105, 272]
	365 (12)				
	394 (13)		≥302		
	450 (15)			≥358	≥273

1. Visit day is the target day.
2. Second study injection only applicable to 2-dose unvaccinated and 3-dose unvaccinated participants.
3. Third study injection only applicable to 3-dose unvaccinated participants. SOT recipients who were previously vaccinated with 2 doses of Moderna COVID-19 vaccine prior to enrollment will receive dose 3 (first study injection) on Day 1.

	Visit Day (Month/Study Visit Day During BD Phase) [1]	Study Injection [2]	Visit Window by Regimen with Booster (Part A + Part B)			
			2-Dose Unvaccinated with Booster	3-Dose Unvaccinated with Booster	3-Dose Previously Vaccinated with Moderna COVID-19 Vaccine with Booster [3]	Previously Vaccinated with COVID-19 Vaccine outside of the study with Booster [4]
NP Swab for SARS-CoV-2	1	First	≤1, Pre-dose	≤1, Pre-dose		
	29 (1)	Second	[2, 43]	[2, 43]		
	57 (2)		[44, End of Part A]	[44, 71]		
	85 (3)	Third		[72, 99]	≤1, Pre-dose	
	113 (4)			[100, End of Part A]	[2, End of Part A]	
	Booster Phase (Part B) [5]					
	BD-Day 1	BD	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster	≤ 1, Pre-booster
Safety Lab	1	First	≤1, Pre-dose	≤1, Pre-dose		
	8		[2, 18]	[2, 18]		
	29 (1)	Second	[19, 32]	[19, 32]		
	36		[33, 46]	[33, 46]		
	57 (2)		[47, End of Part A]	[47, 71]		
	85 (3)	Third		[72, 88]	≤1, Pre-dose	
	92			[89, 101]	[2, 18]	
	113 (4)			[102, End of Part A]	[19, End of Part A]	
	Booster Phase (Part B) [5]					
	BD-Day 1	BD	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster
	BD-Day 8		[2, 18]	[2, 18]	[2, 18]	[2, 18]
	BD-Day 29		≥19	≥19	≥19	≥19
Vital Signs	1	First	≤1, Pre-dose	≤1, Pre-dose		
	1	First	1, Post-dose	1, Post-dose		
	29 (1)	Second	[2, 29 Pre-dose]	[2, 29 Pre-dose]		
	29 (1)	Second	[29 Post-dose, 43]	[29 Post-dose, 43]		
	57 (2)		[44, End of Part A]	[44, 71]		
	85 (3)	Third		[72, 85 Pre-dose]	≤1, Pre-dose	
	85 (3)	Third		[85 Post-dose, 99]	1, Post-dose	
	113 (4)			[100, End of Part A]	[2, End of Part A]	
	Booster Phase (Part B) [5]					

	BD-Day 1	BD	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster
	BD-Day 1	BD	1, Post-booster	1, Post-booster	1, Post-booster	1, Post-booster
	BD-Day 8		[2, 18]	[2, 18]	[2, 18]	[2, 18]
	BD-Day 29		[19, 105]	[19, 105]	[19, 105]	[19, 105]
	BD-Day 181		≥106	≥106	≥106	≥106
Immunogenicity	1	First	≤1, Pre-dose	≤1, Pre-dose		
	29 (1)	Second	[2, 43]	[2, 43]		
	57 (2)		[44, End of Part A]	[44, 71]		
	85 (3)	Third		[72, 99]	≤1, Pre-dose	
	113 (4)			[100, End of Part A]	[2, End of Part A]	
	Booster Phase (Part B) [5]					
	BD-Day 1	BD	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster	≤1, Pre-booster
	BD-Day 29		[2, 105]	[2, 105]	[2, 105]	[2, 105]
	BD-Day 181		≥106	≥106	≥106	≥106

1. Visit day is the target day.
2. Second study injection only applicable to 2-dose unvaccinated with booster and 3-dose unvaccinated participants with booster. Third study injection only applicable to 3-dose unvaccinated participants with booster.
3. SOT recipients who were previously vaccinated with 2 doses of Moderna COVID-19 vaccine will receive dose 3 (first study injection) on Day 1.
4. SOT recipients who were previously vaccinated with mRNA or non-mRNA COVID-19 vaccine primary series (outside of the study) will receive BD (first study injection) on BD-Day 1.
5. Visit window for booster phase (Part B) will be based on booster dose (assessment date – date of BD +1).

Protocol Amendment 3 added the arm that includes 3-dose unvaccinated SOT participants. Since these participants have been previously dosed according to the approved, 2-dose schedule of mRNA-1273, certain summaries will present results from this arm in a manner that aligns their dose 3, which occurs on Day 1 of the study, with the dose 3 received by the unvaccinated SOT participants. This is illustrated in Table 5 below.

Table 4. Alignment of Visits Relative to Dose 3 between Vaccinated and Unvaccinated Participants on the 3-Dose Regimen

	Unvaccinated SOT (3-doses)		Vaccinated SOT (3-doses)	
Dose #	(Visit # / Study Day)	Days Since Most Recent Dose	(Visit # / Study Day)	Days Since Most Recent Dose
Dose 1	Visit 1 / Day 1	0		
	Visit 2 / Day 8	7		
Dose 2	Visit 3 / Day 29	0		
	Visit 4 / Day 36	7		
	Visit 5 / Day 57	28		
Dose 3	Visit 6 / Day 85	0	Visit 1 / Day 1	0
	Visit 7 / Day 92	7	Visit 2 / Day 8	7
	Visit 8 / Day 113	28	Visit 3 / Day 29	28
	Visit 9 / Day 265	180	Visit 4 / Day 180	180
	Visit 10 / Day 450	365	Visit 5 / Day 365	365

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

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

1. Missing or partial medication start date:

- If only Day is missing, use the first day of the month, unless:
  - The medication end date is after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection
- If Day and Month are both missing, use the first day of the year, unless:
  - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection
- If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.

2. Missing or partial medication stop date:

   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

9.4. Appendix D Imputation Rules for Missing AE dates

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

1. Missing or partial AE start date:

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

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

9.5. Appendix E. Schedule of Events

Refer to Table 7, Table 8, Table 9, and Table 18 in Appendix 1 (Schedule of Events) in Protocol Amendment 4.

9.6. Appendix F. Severity Grading of Laboratory Abnormalities

Table 5. 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 Preventive Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Table 6. 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).

9.7. Appendix G. Immunogenicity Assessments

The following laboratory assays are planned to measure the immune response to mRNA-1273:

Table 7. Antibody Immunogenicity Assessments

Material	Component	Assay	Method
Serum	Neutralizing Antibodies	VAC 62 Pseudovirus Neutralizing Antibody	Psudovirion-based neutralization assay
Serum	Binding Antibodies	VAC 123 IgG antibodies against SARS-CoV-2 Spike Protein, Variants (Omicron, and etc.), Receptor-Binding Domain, and Nucleocapsid* Protein	MSD Multiplex

Abbreviations: MSD = Meso Scale Discovery.
*Seroresponse will not be performed for the binding antibody testing against anti-nucleocapsid by MSD multiplex assay.