CLINICAL STUDY PROTOCOL

Protocol Title:	Randomized, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults
Protocol Number:	mRNA-1273-P401
Amendment Number:	2
Amendment Scope:	Global
Compound:	mRNA-1273.815
Brief Title:	A Study to Investigate Immunogenicity of an Investigational mRNA-1273.815 in Previously Vaccinated Adults
Study Phase:	Phase 3b
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number(s):	**Registry** **ID** **N/A** **N/A**
Date:	27 FEB 2024

Sponsor Signatory:

See e-Signature and date signed on last page the document.

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "Randomized, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults" dated 27 FEB 2024 and the most recent version of the mRNA-1273 Investigator's Brochure.

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

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

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

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

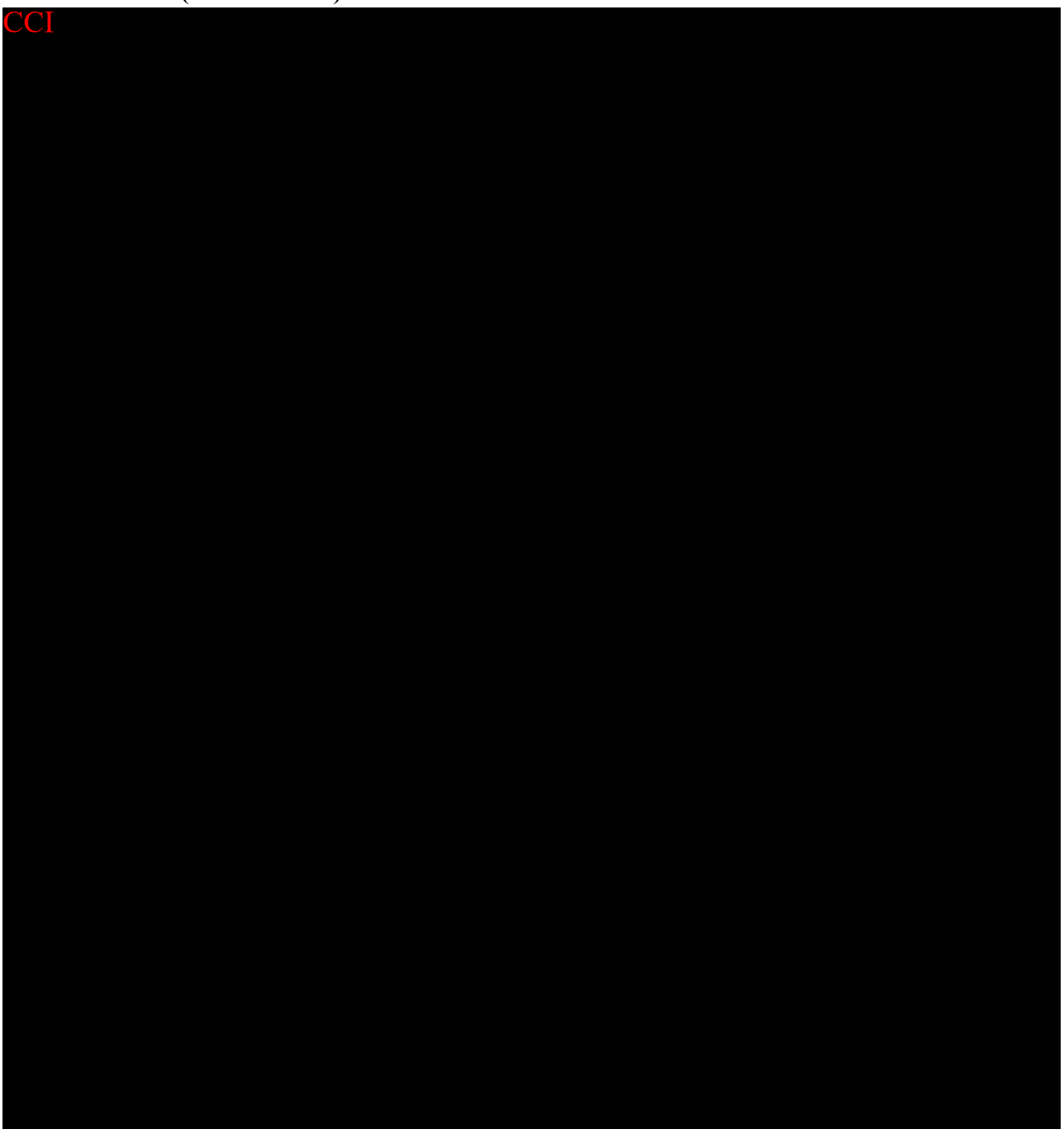
Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	27 FEB 2024
Amendment 1	11 JAN 2024
Original Protocol	13 OCT 2023

Amendment 2 (27 FEB 2024)

CCI



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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
AE	Adverse event
AR	Adverse reaction
AESI	Adverse event of special interest
bAb	Binding antibody
BD	Booster dose
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac event adjudication committee
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cMRI	Cardiac magnetic resonance imaging
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
DHHS	Department of Health and Human Services
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG/EKG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End-of-study
EUA	Emergency Use Authorization
EVCTM	EudraVigilance Clinical Trial Module
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	Gamma-glutamyl transferase
GM	Geometric mean
GMFR	Geometric mean fold-rise
GMR	Geometric mean ratio
GMT	Geometric mean titer
HELLP	Hemolysis, elevated liver enzymes, and low platelets
HLH	Hemophagocytic lymphohistiocytosis
HREC	Human Research Ethics Committee
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICSR	Individual case safety report(s)
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive web response system
LAM	Lactational amenorrhea method
LLOQ	Lower limit of quantitation
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
N (or n)	Number of subjects
nAb	Neutralizing antibody
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
POCBP	Person of childbearing potential
PONCBP	Person of nonchildbearing potential
PP	Per-protocol
PPIS	Per-protocol Immunogenicity Subset

Abbreviation	Definition
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
S-2P	Spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SM-102	Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SoA	Schedule of Activities
SRR	Seroresponse rate
SUSAR	Suspected unexpected serious adverse reaction
US	United States
XBB.1.5	Omicron subvariant strain of SARS-CoV-2

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

Randomized, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults

Regulatory Agency Identifier Number(s):

Registry	ID
N/A	N/A

Rationale:

In mRNA vaccine manufacturing, the RNA sequence is encapsulated by LNP. Percent RNA encapsulation is a critical quality attribute for mRNA-1273 LNP. The LNP acts as a delivery vehicle and protectant for the RNA and is essential for biological activity of a drug product as well as stability of the RNA. The percent RNA encapsulation is defined as the percent of RNA entrapped in LNPs relative to the total amount of RNA. Vaccine manufacturing processes can occasionally result in variations in percent RNA encapsulation between different manufacturing lots, leading to differences in vaccine specifications. Nonclinical data in mice demonstrate comparable immunogenicity of mRNA-1273 over a range of percent RNA encapsulation CCI [redacted]

The rationale for conducting the study is to generate clinical data to support widening the percent RNA encapsulation lower-limit from that which is currently approved for mRNA-1273.815 against the XBB.1.5 strain (hereafter referred to as licensed Spikevax) and its variant-encoding formulations. Accordingly, this study aims to confirm findings from the nonclinical study by evaluating immunogenicity of an investigational mRNA-1273.815 COVID-19 vaccine with a wider percent RNA encapsulation lower-limit (hereafter referred to as Investigational mRNA-1273.815 or IMP) compared to the licensed Spikevax. Note that the percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than C [redacted] lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5.
CI

Data generated from the study may also contribute to knowledge and understanding of the mRNA LNP and its effect on vaccine-elicited immunogenicity.

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain	• GM value of nAb against XBB.1.5 at Day 15

Objectives	Endpoints
Secondary	
• To evaluate the safety of the CCI-µg licensed Spikevax or Investigational mRNA-1273.815	• SAEs, AESIs, and AEs leading to withdrawal from the study on Day 1 through 15 days after injection
• To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain	• SRR of nAb against the XBB.1.5 strain at Day 15, where seroresponse is defined as nAb value change from baseline (preinjection Day 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ • GMR of nAb against the XBB.1.5 at Day 15 between the 2 treatment groups

Abbreviations: AE = adverse event; AESI = adverse event of special interest; GM = geometric mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; SAE = serious adverse event; SRR = seroresponse rate.

Overall Design Synopsis:

The study is a Phase 3b, randomized, observer-blind, active-controlled, clinical study to assess the immunogenicity of an Investigational mRNA-1273.815 COVID-19 vaccine in previously vaccinated adults. Randomization will be stratified by age (18 to <65 years, and ≥65 years).

The study comprises 3 scheduled in-clinic visits including a Screening Visit (Screening and dosing can be performed on the same day) per Section 1.2 and Section 1.3. This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

In this multisite study, participants will be randomized to either licensed Spikevax or Investigational mRNA-1273.815 with a wider RNA encapsulation lower-limit specification. The percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IMP administered on Day 1 until study end.

With SARS-CoV-2 expected to be circulating in the general population during the study, blood samples will be tested at baseline (preinjection Day 1) for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2.

To assess the vaccine-induced immune responses, blood samples will also be collected from all participants on Day 1 (preinjection) and Day 15 for measurement of SARS-CoV-2 specific nAb responses.

In addition, participants will have nasal swab samples collected before the injection on Day 1 as well as on Day 15.

To monitor for safety, safety data will be collected and will include SAEs, and AESIs, and AEs leading to discontinuation from study participation.

Number of Participants:

Approximately 200 adult (≥18 years of age) participants will be enrolled and randomized (1:1) to licensed Spikevax or Investigational mRNA-1273.815.

Study Duration:

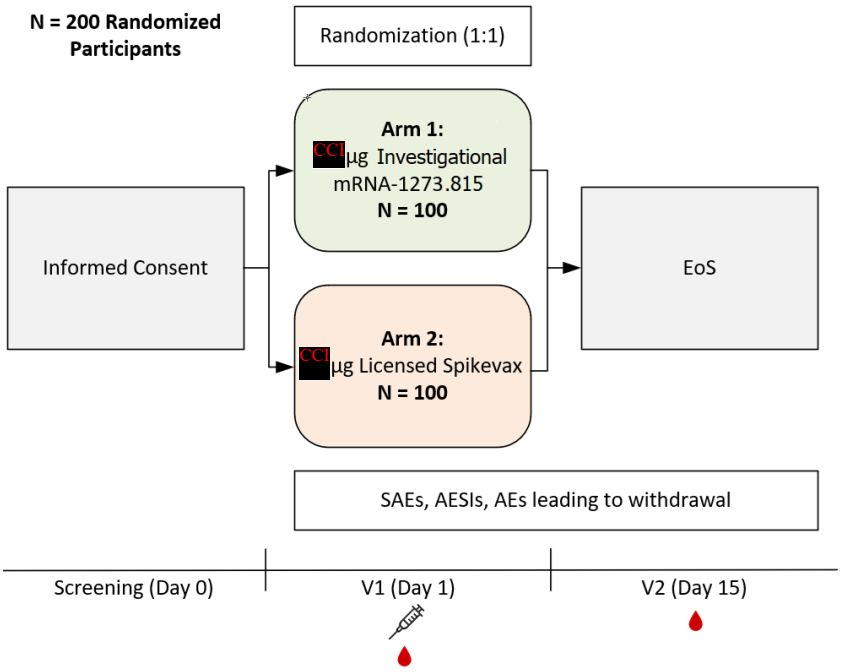
Participants will be in the study for approximately 2 weeks, which includes 7 days for Screening (Day -7 to Day 1), 1 day of dosing (Day 1), and 2 weeks of follow-up.

Study Treatment:

CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 injection (administered intramuscularly).

1.2. Schema

Figure 1: Schema of Study Design



Abbreviations: AE = adverse event; AESI = adverse event of special interest; EoS = end-of-study; V = visit; mRNA = messenger ribonucleic acid; N = number of participants; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: the percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5.

Study Injection

Blood for SARS-CoV-2 serology (antinucleocapsid antibody) at Day 1 and for immune response to injection (Day 1 [preinjection] and Day 15).

1.3. Schedule of Activities

Table 2: Schedule of Activities

Visit Number	Screening[1]	V1	V2 (EoS)	UNS[2]
Type of Visit	C	C	C	C
Study Visit Day	D0[1]	D1[1]	D15	N/A
Window Allowance (Days)	-7	0	±3	N/A
Days Since Injection	N/A	0	14	N/A
Informed consent form	X			
Randomization, study injection (including 30-minute post-injection observation period)		X		
Confirm participant meets inclusion and exclusion criteria	X			
Physical examination including vital signs[3]	X	X	X	X
Pregnancy testing		X		
Blood for SARS-CoV-2 serology (antinucleocapsid antibody)[4]		X		
Blood for immune response to vaccination[5]		X	X	
Nasal swab sample for SARS-CoV-2[4]		X	X	
Recording of SAEs, AESIs, AEs leading to withdrawal and concomitant medications relevant to or for the treatment of the SAEs, AESIs, and AEs leading to withdrawal[6]		X	X	X
Recording of concomitant medications and nonstudy vaccinations[7]		X	X	X
Study completion			X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = clinic visit; D = day; EoS = end-of-study; ICF = informed consent form; IMP =investigational medicinal product; M = month; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UNS = unscheduled visit; V = visit.

1. The Screening Visit and Day 1 (study injection) Visit can be combined and occur on the same day. Collection of SAEs, AESIs, and AEs leading to withdrawal will begin after signing of ICF.

2. A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by new or ongoing AEs. The study site also has the discretion to make safety telephone calls or send text messages to remind the participant about visits, or follow-up on ongoing or outstanding issues.
3. Physical examination: A full physical examination, including height and weight, will be performed on Day 1. Symptom-directed physical examinations may be performed at other timepoints at the discretion of the Investigator. Vital signs (Section 8.2.4) are to be collected pre- and post-injection on the day of injection (Day 1) only. When applicable, vital sign measurements should be performed before blood collection. For participants who are febrile (body temperature ≥38.0°C [100.4°F]) before injection on Day 1, the visit must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be administered IMP at the discretion of the Investigator.
4. Blood samples will be tested at baseline (preinjection Day 1) for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2. In addition, the nasal swab sample, collected prior to injection on Day 1, will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
5. Blood samples will be collected from all participants on Day 1 (preinjection) and Day 15 for measurement of SARS-CoV-2 specific nAb responses.
6. All concomitant medications relevant to or for the treatment of an SAE, AESI, and AE leading to withdrawal will be recorded from Day 1 through the EoS Visit.
7. All concomitant medications and nonstudy vaccinations will be recorded through EoS Visit.

2. INTRODUCTION

2.1. Study Rationale

In mRNA vaccines, the RNA is encapsulated in LNPs to facilitate intracellular delivery of the mRNA. RNA encapsulation is an mRNA vaccine product attribute defined as the percent of RNA entrapped in LNPs relative to the total amount of RNA.

Variability in mRNA vaccine manufacturing processes can occasionally result in variations in RNA encapsulation between different manufacturing lots. Nonclinical data in mice demonstrate comparable immunogenicity of mRNA-1273 over a range of percent RNA encapsulation CCI [redacted]. The rationale for conducting the study is to generate clinical data to support widening the percent RNA encapsulation lower-limit from that which is currently approved for mRNA-1273.815 against the XBB.1.5 strain (hereafter referred to as licensed Spikevax) and its variant-encoding formulations. Accordingly, this study aims to confirm findings from the nonclinical study by evaluating immunogenicity of an investigational mRNA-1273.815 COVID-19 vaccine with a wider percent RNA encapsulation lower-limit (hereafter referred to as Investigational mRNA-1273.815 or IMP) compared with the licensed Spikevax. Note that the percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine. The investigational mRNA-1273.815 is otherwise the same as the licensed Spikevax, including the dosage and the Omicron subvariant XBB.1.5 content.

2.2. Background

The Sponsor's mRNA/LNP platform is based on the principle and observations that cells *in vivo* can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA-1273 encodes for the full-length spike (S) protein SARS-CoV-2(CoV S). The CoV S protein mediates attachment and entry of the virus into host cells by binding to the angiotensin converting enzyme 2 receptor followed by membrane fusion, making it a primary target for nAb that prevents infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020).

The Sponsor's scalable mRNA/LNP technology platform allowed for a rapid response to the COVID-19 pandemic and was used to develop mRNA-1273, an LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. Occasionally, variability in the manufacturing process is expected and could result in differences in product attributes, including percent RNA encapsulation that represents the percent of total RNA entrapped within LNPs. RNA that is not encapsulated in an LNP will not efficiently enter cells to be translated to the target protein.

The Sponsor has previously demonstrated vaccine efficacy of a 2-dose CCI µg mRNA-1273 primary series in the pivotal efficacy study in adults (P301) (Baden et al 2021; El Sahly et al 2021). An immunobridging strategy has also been used to provide evidence of vaccine effectiveness of mRNA-1273 booster and variant-encoding formulations (Chalkias et al 2022a). In addition, mRNA-1273 and variant-encoding formulations were well-tolerated with a favorable risk-benefit profile (see IB detailed description of safety data).

More recently, clinical data on the updated mRNA-1273.815 (Spikevax), an LNP-encapsulated, mRNA-based vaccine containing CCI µg RNA encoding the S-2P of the Omicron XBB.1.5 subvariant, demonstrate that the vaccine was well-tolerated and induced robust neutralizing responses to Omicron XBB variants, previous strains including ancestral and Omicron BA.4/BA.5, and more recently emerging strains.

Worldwide approvals or authorizations have been issued for mRNA-1273 as a 2-dose CCI-µg primary series or as a CCI-µg BD across age groups. Moderna variant-encoding bivalent booster vaccines (mRNA-1273.214 and mRNA-1273.222) have also received approvals or authorizations globally across age groups in 2022. Beginning in Sep 2023, the Spikevax vaccine encoding for the WHO, EMA, and FDA recommended composition of monovalent XBB.1.5 for 2023-2024 has received approvals in the US, EU, Japan, and other countries worldwide.

Method of RNA Encapsulation:

RNA is encapsulated within LNPs by charge capture, whereby the negative charge on the RNA backbone interacts with the positive charge on the SM-102 lipid. Buffers are added to the RNA-lipid complex to further modify the solution pH to physiological levels and generate the final LNP.

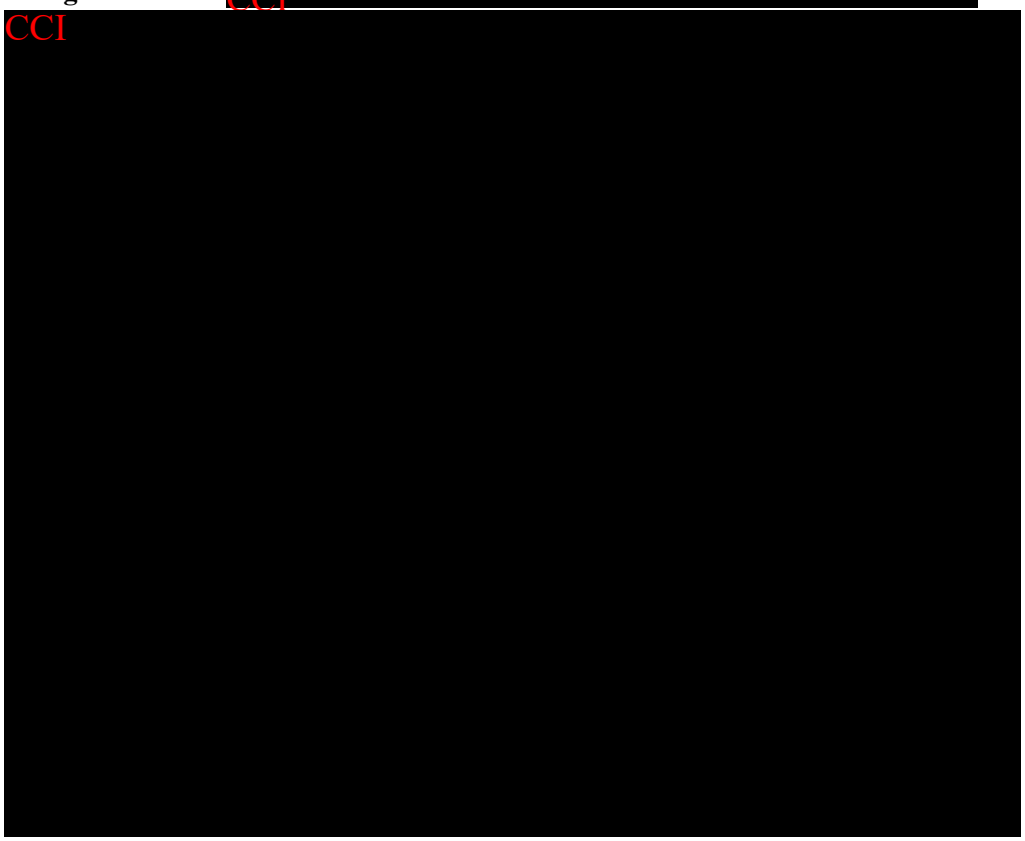
Impact of RNA Encapsulation on Protein Expression:

Encapsulation of RNA in the LNP protects the RNA from degradation and facilitates cellular uptake and endosomal escape. Unencapsulated (free) RNA is not a safety concern, since it is quickly degraded by the high levels of RNase activity, which limits the half-life of free mRNA in human extracellular space. RNA that is not encapsulated in an LNP will not efficiently enter cells to be translated to the target protein.

Nonclinical Data Supporting Widening the Percent RNA Encapsulation Lower-limit Specification:

A nonclinical study was conducted in BALB/c mice to evaluate the immunogenicity of mRNA-1273 with variable levels of encapsulation CCI BALB/c mice were given a 2-dose series, with readouts at Day 21 and Day 36 across 3 different dose levels CCI The geometric mean titers and interquartile ranges of all encapsulation levels were within 0.5 log of the control group CCI demonstrating the comparability of immunogenicity across a range of encapsulation levels. In addition, the geometric mean titer ratios (Figure 2) compared to the control sample are shown at Day 21 and Day 36 across each dose range. All samples were within the 3-fold variability range for all doses at Day 21 and Day 36. Most of the samples tested were also within the narrower 2-fold variability range. Results from this nonclinical study demonstrate broad immunogenicity of the mRNA-1273 vaccine over a range of encapsulation and support that the encapsulation levels evaluated do not impact product immunogenicity. Based on previous analyses demonstrating that mouse immunogenicity is consistent with human immune responses to mRNA-1273 vaccines (Chalkias et al 2022b; Chalkias et al 2023; Scheaffer et al 2023; Wu et al 2021), the mouse immunogenicity data are reasonably likely to predict comparable immunogenicity in humans.

Figure 2: CCI



A detailed review of nonclinical and clinical experience with mRNA-1273 vaccine and variant-encoding formulations are provided in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mRNA-1273 and variant-containing formulations may be found in the IB.

2.3.1. Risk Assessment

As with all injectable vaccines, immediate systemic allergic reactions to vaccination, ranging from mild (eg, urticaria) to severe (eg, anaphylaxis) can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

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

As with other IM injections, the study vaccines should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as hemophilia) because bleeding or bruising may occur following an IM administration in these individuals.

Local ARs are expected after IM injection. These are typically mild, transient, and self-limited and may include pain, erythema (redness), or swelling/induration (hardness) at the injection site and/or ipsilateral underarm swelling/tenderness.

Systemic ARs may also occur after study intervention administration, the majority of which are of mild to moderate in severity. Systemic ARs reported with mRNA-1273 vaccines may include fatigue, headache, myalgia, fever, chills, arthralgia, vomiting and/or nausea.

There have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis (Section 10.4) occurring after injection with COVID-19 mRNA vaccines. The majority of the cases have been reported in adolescent and young males, within 7 to 14 days after the second or subsequent injections. These are typically mild cases, and individuals tend to recover within a short time following conservative treatment. Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

Safety Considerations for Unencapsulated RNA:

Unencapsulated RNA is not a safety concern, since RNA that is not encapsulated in an LNP will not efficiently enter cells to be translated to the target protein and is quickly degraded by the high levels of RNase activity, limiting the half-life of free mRNA in human extracellular space.

The impact of free mRNA on mice CCI [redacted] was evaluated *in vivo* CCI [redacted] No SAEs were reported in any of the mice over the duration of the study, and the weight of each test animal was consistent throughout the study suggesting that the free mRNA was well-tolerated. No immune response to mRNA-1273 was measured in any of the study groups, suggesting that the free mRNA cellular uptake is negligible due to rapid degradation *in vivo*.

Free mRNA has also been evaluated clinically using a lyophilized mRNA vaccine for Rabies glycoprotein (Alberer et al 2017). The vaccine was comprised of 50% free mRNA and 50% mRNA complexed with protamine, a known enhancer of viral transduction. The Phase 1 study evaluated doses of 80 mcg to 640 mcg delivered both IM and intradermally, representing over an order of magnitude greater free mRNA exposure compared to the exposure levels CCI [redacted] for mRNA-1273. The Investigators reported that the vaccine was generally well tolerated across the evaluated dose range, with typical local site reactions and AEs including fatigue, nausea, fever, and chills reported by some participants.

2.3.2. Benefit Assessment

Currently, there is no clinical experience with mRNA-1273 vaccine lots with reduced lower-limits of percent RNA encapsulation. However, in nonclinical and clinical data from a number of mRNA-1273 variant-encoding vaccines, the immune responses observed in humans were consistent with the immune responses observed in corresponding mice models (Chalkias et al 2022b; Chalkias et al 2023a; Scheaffer et al 2023; Wu et al 2021). Similarly, it is expected that the mouse immunogenicity study that demonstrated the comparability of immunogenicity across a range of encapsulation levels CCI [redacted] is likely to predict comparable immunogenicity in humans at the reduced lower-limit of percent RNA encapsulation of the IMP.

The following benefits may accrue to participants:

- Licensed Spikevax vaccine may protect against COVID-19 including disease caused by variants of concern.
- The Investigational mRNA-1273.815 vaccine may be effective against COVID-19 including disease caused by variants of concern.
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection.
- Data generated from the study may also contribute to knowledge and understanding of the mRNA LNP and its effect on vaccine-elicited immunogenicity.

2.3.3. Overall Benefit/Risk Conclusion

All participants will receive either a single dose of [redacted] µg licensed Spikevax vaccine or Investigational mRNA-1273.815 vaccine.

Safety will be monitored throughout the study (Section 8.2).

Considering that 1) no safety concerns are anticipated, 2) the immunogenicity of the Investigational mRNA-1273.815 vaccine is anticipated to be comparable with the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5, and 3) participants' risk of COVID-19 outside the study, the Sponsor considers the potential benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain	• GM value of nAb against XBB.1.5 at Day 15
Secondary	
• To evaluate the safety of the CCI-µg licensed Spikevax or Investigational mRNA-1273.815	• SAEs, AESIs, and AEs leading to withdrawal from the study on Day 1 through 15 days after injection
• To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain	• SRR of nAb against the XBB.1.5 strain at Day 15, where seroresponse is defined as nAb value change from baseline (preinjection Day 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ • GMR of nAb against the XBB.1.5 at Day 15 between the 2 treatment groups

Abbreviations: AE = adverse event; AESI = adverse event of special interest; GM = geometric mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; SAE = serious adverse event; SRR = seroresponse rate.

4. STUDY DESIGN

4.1. Overall Design

The study is a Phase 3b, randomized, observer-blind, active-controlled, clinical study to assess the immunogenicity of an Investigational mRNA-1273.815 COVID-19 vaccine in previously vaccinated adults. Randomization will be stratified by age (18 to <65 years, and ≥65 years).

The study comprises 3 scheduled in-clinic visits including a Screening Visit (Screening and dosing can be performed on the same day) per Section 1.2 and Section 1.3. This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

In this multisite study, participants will be randomized to either licensed Spikevax or Investigational mRNA-1273.815 with a wider RNA encapsulation lower-limit specification. The percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IMP administered on Day 1 until study end.

With SARS-CoV-2 expected to be circulating in the general population during the study, blood samples will be tested at baseline (preinjection Day 1) for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2.

To assess the vaccine-induced immune responses, blood samples will also be collected from all participants on Day 1 (preinjection) and Day 15 for measurement of SARS-CoV-2 specific nAb responses.

In addition, participants will have nasal swab samples collected before the injection on Day 1 as well as on Day 15.

To monitor for safety, safety data will be collected and will include SAEs, and AESIs, and AEs leading to discontinuation from study participation.

4.2. Scientific Rationale for Study Design

This is a descriptive Phase 3b study designed as a randomized, observer-blind, active-controlled, clinical study to assess the immunogenicity of Investigational mRNA-1273.815 vaccine compared to the licensed Spikevax vaccine, both containing the updated XBB.1.5 strain, in previously vaccinated adults.

This study is being conducted to generate clinical data to support widening the percent RNA encapsulation lower-limit specification. Data generated from the study may also contribute to knowledge and understanding of the mRNA LNP and its effect on vaccine-elicited immunogenicity.

4.3. Justification for Dose

The CCI-µg dose level of the Investigational mRNA-1273.815 is the same as the current dose for licensed Spikevax.

The percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5.

Nonclinical data demonstrate comparable immunogenicity (nAb GMTs) of mRNA-1273 over a range of percent RNA encapsulation CCI [redacted] (Section 2.2). Mouse immunogenicity has also been shown to be consistent with human immune responses to mRNA-1273 vaccines (Chalkias et al 2022b; Chalkias et al 2023a; Scheaffer et al 2023; Wu et al 2021). Accordingly, it is anticipated that Investigational mRNA-1273.815 vaccine will have similar immunogenicity as licensed Spikevax.

4.4. End-of-Study Definition

The EoS is defined as the date when last data are available.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female, at least 18 years of age at the time of consent (Screening Visit) who previously received:
   a. At least 2 COVID-19 vaccines as primary series (mRNA or non-mRNA or a combination of both) AND
   b. At least 1 mRNA booster dose (third dose).
2. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
3. Participant has provided written and signed informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Investigator's assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
5. PNCBP may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥12 consecutive months prior to Screening [Day 0] without an alternative medical cause). A FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. POCBP may be enrolled in the study if the participant fulfills all of the following criteria:
   a. Has a negative pregnancy test on the day of injection prior to vaccine dose being administered (Day 1).
   b. Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
   c. Has agreed to continue using an effective contraception through 2 weeks following injection.

      Note: a list of acceptable contraceptive methods is listed in Section 10.3.

   d. Is not currently breastfeeding.

   Adequate female contraception is defined as consistent and correct use of a contraceptive method approved by US FDA (Section 10.3) or local health agency in accordance with the product label.

5.2. Exclusion Criteria

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

1. Has known history of SARS-CoV-2 infection within 3 months prior to enrollment.

2. Is acutely ill or febrile (temperature ≥38.0°C/[100.4°F]) less than 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled and will retain their initially assigned participant number.
3. Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care, to include significant change in therapy or hospitalization for worsening disease, at the discretion of the Investigator.

   Clinically unstable is defined as a diagnosis or condition requiring changes in management or medication within the 60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

   Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immunosuppressive treatments), at the discretion of the Investigator.
4. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the Investigator's judgment.
5. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunosuppressive condition, asplenia, or recurrent severe infections disease.
6. Has known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.
7. History of Guillain-Barré syndrome.
8. Has a documented history of myocarditis or pericarditis within 2 months prior to Screening Visit (Day 0).
9. Coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.
10. Receipt of the following:
    a. COVID-19 vaccine within 3 months prior to enrollment
    b. Any other licensed vaccine within 28 days before or 2 weeks after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.
    c. Systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.

       Note: Inhaled, nasal, and topical steroids are allowed.

    d. Systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (Day 0) or plans for receipt during the study.

11. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
12. Has participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.
13. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

5.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Once rescreened, participants should be assigned a new participant number for every Screening/Rescreening event.

5.4. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Body temperature (oral) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the relevant SoA (Section 1.3), or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7.2):

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

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

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the Investigator and the CRO's medical monitor (Section 6.9.2).

6. STUDY INTERVENTION(S)

6.1. Study Intervention(s) Administered

The IMP in mRNA-1273-P401 is either the Investigational mRNA-1273.815 (CCI µg) vaccine or the licensed Spikevax (CCI µg) vaccine. Both IMPs use the Sponsor's mRNA-LNP technology platform.

The Investigational mRNA-1273.815 and the licensed Spikevax are both an RNA-LNP dispersion consisting of RNA encoding the S-2P of the SARS-CoV-2 XBB.1.5 subvariant of Omicron, formulated in a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

Investigational mRNA-1273.815 or licensed Spikevax will be provided as a sterile solution for injection at a concentration of CCI [redacted] The IMP is packaged in 2R USP Type I borosilicate glass vials with a PLASCAP® vial seal containing a 13 mm FluroTec®-coated plug stopper with a 0.65 mL nominal fill volume.

Study Intervention Packaging and Labeling:

The Sponsor will provide the Investigator (via the study site pharmacy) with adequate quantities of IMP. The sterile IMP is packaged in 2R glass vials with a 0.65 mL nominal fill volume. The IMP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

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

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Preparation of Study Vaccine for Injection

Each dose of IMP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P401 Pharmacy Manual. The volume of IMP injected will be 0.5 mL consisting of either a CCI-µg dose of Investigational mRNA-1273.815 or a CCI-µg dose of the licensed Spikevax, as detailed in the mRNA-1273-P401 Pharmacy Manual.

6.2.2. Administration of Study Vaccine

Each participant will receive 1 dose of IMP by IM injection according to their assigned regimen and according to the procedures specified in the mRNA-1273-P401 Pharmacy Manual.

At each visit when IMP is administered, participants will be monitored for a minimum of 30 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (Section 1.3).

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

6.2.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IMP.
- Confirming the appropriate labeling of the IMP, so that it complies with the legal requirements of study countries.

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

- Confirming that the IMP was received in good condition.
- Confirming that the temperature during shipment from the Sponsor to the Investigator's designated storage location was appropriate.
- Confirming that the Sponsor has authorized the IMP for use.
- Ensuring the appropriate dose level of IMP is properly prepared using aseptic technique.

Further description of the IMP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IMP are described in the mRNA-1273-P401 Pharmacy Manual.

6.2.4. Study Vaccine Storage

The IMP must be stored as per the temperature conditions printed on the IMP label in a secure area with limited access and protected from moisture and light until it is prepared for administration (Section 6.2.1). The refrigerator and/or freezer utilized for IMP storage should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator and/or freezer malfunction. There must be an available backup refrigerator and freezer. The refrigerators and freezers must be connected to a backup generator(s). In addition, IMP accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IMP that was not temperature controlled during shipment or during storage.

6.2.5. Study Vaccine Accountability

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

A study site monitor will review the inventory and accountability log during study site visits and at the completion of the study. Additional details are found in the mRNA-1273-P401 Pharmacy Manual.

6.2.6. Study Vaccine Handling and Disposal

A study site monitor will reconcile the IMP inventory during the conduct and at the end of the study for compliance. Once fully reconciled at the study site at the end of the study and approved

by the Sponsor, the IMP will be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

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

6.3. Assignment to Study Intervention

Random assignment of participants will use a centralized interactive response technology, in accordance with pre-generated randomization schedules.

6.4. Blinding

This study is an observer-blind study.

6.4.1. Unblinding

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer the Investigational mRNA-1273.815 or licensed Spikevax to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of IMP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded study site monitors, not involved in other aspects of monitoring, will be assigned as the IMP accountability monitors. They will have responsibilities to ensure that study sites are following all proper IMP accountability, preparation, and administration procedures.

6.4.2. Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the Investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The Investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

6.5. Study Intervention Compliance

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

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Section 1.3). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

6.6. Dose Modification

A single CCI-µg dose of Investigational mRNA-1273.815 or licensed Spikevax will be administered to participants. Criteria for delaying or discontinuing vaccine administration are provided in Section 7.

6.7. Continued Access to Study Intervention After the EoS

Any SAE occurring after the end of study and considered to be caused by the IMP must be reported to the Sponsor.

6.8. Treatment of Overdose

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

6.9. Prior and Concomitant Therapy

6.9.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent/assent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF. All previous COVID-19 vaccinations received prior to informed consent/assent will be recorded.

6.9.2. Recording of Concomitant Medications and Concomitant Vaccinations

At each study visit, study site staff must question the participant and/or the participants' parent(s)/LAR(s) regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IMP.
- Seasonal influenza vaccine administered 28 days before the IMP.

- All concomitant medications and nonstudy vaccinations taken through 15 days after dose of IMP. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or AE leading to withdrawal.
- Participants will be asked if they have taken any antipyretic or analgesic to treat or prevent fever or pain on the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the post-injection study visits or via other participant interactions (eg, phone calls, if needed).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the Investigator and the CRO's medical monitor will make a joint decision about continuing or withholding injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the Investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

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

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study, but may determine a participant's evaluability in the PP analyses (analysis sets are described in Section 9.3):

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1. Discontinuation of Study Intervention

A single dose of the IMP will be administered on Day 1. No further injections will be administered. See Section 5.4 for criteria for temporarily delaying study injection.

The Investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from study injection if the participant experiences any of the following prior to injection on Day 1:

- Becomes pregnant.
- Withdrawal of consent (not related to COVID-19).
- Develops symptoms or conditions listed in the exclusion criteria (Section 5.2).

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

7.2. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol. The statistical management of participant withdrawals is discussed in Section 9.

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

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

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

- AE (specify)
- SAE (specify)
- Death
- Lost to follow-up
- Physician decision (specify)
- Pregnancy
- Protocol deviation

- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

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

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

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

7.3. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF (as detailed in Section 10.1.3). Participants will undergo study procedures at the timepoints specified in the SoA (Section 1.3).

A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by new or ongoing AEs. The study site also has the discretion to make safety telephone calls or send text messages to remind the participant about visits or follow up with ongoing or outstanding issues.

In accordance with regulatory authority guidance, Investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Section 1.3. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

8.1. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Section 1.3).

The following analytes will be measured in blood samples for immunogenicity assessments:

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

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

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

- AEs leading to withdrawal from the study.
- AESIs from vaccination on Day 1 through EoS.
- SAEs from vaccination on Day 1 through EoS.
- Vital sign measurements before and after vaccination.
- Physical examination findings (including if performed after initial exam).

- Details of all pregnancies (Section 10.2.2) in female participants will be collected after the start of study treatment and until the end of their participation in the study. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after the end of the study may not be collected in the clinical database.
- Concomitant medications and nonstudy vaccinations.

8.2.1. Safety Phone Calls

A safety telephone call is a telephone call made to the participant by trained study site personnel.

The study has the discretion to make reminder telephone calls or send text messages to inform the participant about visits or follow-up on ongoing or outstanding issues (Section 1.3).

The participant may be asked about the occurrence of SAEs, AESIs, AEs leading to withdrawal, concomitant medications relevant to or for the treatment of the SAEs, AESIs, and AEs leading to withdrawal, and any nonstudy vaccinations (Section 8.2). All safety information collected from the telephone contact must be documented in source documents as described by the participant. As noted in Section 8, an unscheduled follow-up safety telephone call may be triggered by identification of a relevant safety event.

8.2.2. Use of Electronic Diaries

No eDiaries will be used in this study.

8.2.3. Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled timepoints as indicated in the SoA (Section 1.3). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities.

Symptom-directed physical examinations may be performed at other timepoints at the discretion of the Investigator.

Body mass index will be calculated at the Screening Visit (Day 0) only.

8.2.4. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the timepoints indicated in the SoA (Section 1.3). At dosing visits, vital sign measurements will be collected once before injection and at least 30 minutes post injection (before participants are discharged from the study site).

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

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

8.2.5. Clinical Safety Laboratory Tests

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1 and Phase 2 studies of mRNA-1273 in adults.

8.2.6. Pregnancy Testing

A point-of-care urine pregnancy test will be performed at the Visit 1 (Day 1) before vaccine dose. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the Investigator.

8.2.7. Assessment for SARS-CoV-2 Infection

Study participants will have nasal swab samples collected for SARS-CoV-2 testing at timepoints specified in the SoA (Section 1.3).

Serum collected from all participants will be tested for bAb against SARS-CoV-2 nucleocapsid protein at Day 1.

8.3. AEs: Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions of AEs, SAEs, SUSARs, and AESIs, are provided in Section 8.3.1. The time period and frequency for collecting safety information is provided in Section 8.3.2. The method of detecting AEs and SAEs is provided in Section 8.3.3. The method of recording AEs and SAEs is described in Section 8.3.4. The assessment of severity (or intensity) and causality is provided in Section 8.3.5. The follow-up of AEs and SAEs is described in Section 8.3.6. The reporting of SAEs/AESIs is described in Section 8.3.7. Regulatory reporting requirements are provided in Section 8.3.8. Pregnancy reporting is provided in Section 8.3.9.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

AEs related to pregnancies, as described in Section 8.3.9, and AEs as a result of medication errors, including overdose, as described in Section 6.8, are subject to AE collection/reporting rules.

8.3.1. Safety Events

AEs are defined in Section 8.3.1.1. SAEs are defined in Section 8.3.1.2. SUSARs are defined in Section 8.3.1.3. AESIs are defined in Section 8.3.1.4.

8.3.1.1. Adverse Event

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

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

8.3.1.2. Serious Adverse Event

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

a. Results in death.

b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity.
- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

d. If exposure to a study intervention prior to conception or during pregnancy may have resulted in birth defects, congenital disorders, congenital malformations, or congenital abnormalities.

e. Other situations:

- Important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

8.3.1.3. Suspected Unexpected Serious Adverse Reaction

A SUSAR is an AE that occurs in a clinical study participant, which is assessed by the Sponsor and/or the Investigator as being unexpected, serious, and having a reasonable possibility of a causal relationship with the study intervention.

Unexpected refers to an AE that is not listed in the IB or is not listed at the severity (or intensity) that has been observed, or not consistent with the applicable Sponsor's product information.

8.3.1.4. Adverse Event of Special Interest

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

The Investigator's medical judgment must be applied to assess an event as an AESI, as most AESIs are based on medical concepts. Table 4 does not provide a comprehensive list of terms.

Table 4 describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per-protocol, even when they occur during/following COVID infection.

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

Table 4: Adverse Events of Special Interest (COVID-19 Vaccines)

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

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

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

Abbreviations: µmol = micromole(s); ADEM = acute disseminated encephalomyelitis; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARDS = Acute Respiratory Distress Syndrome; AST = aspartate aminotransferase; COVID-19 = Coronavirus disease 2019; DIC = disseminated intravascular coagulation; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; DVT = deep vein thrombosis; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; HELLP = hemolysis, elevated liver enzymes, and low platelets; HLH = hemophagocytic lymphohistiocytosis; MIS-A = multisystem inflammatory syndrome in adults; MIS-C = multisystem inflammatory syndrome in children; PCR = polymerase chain reaction.

8.3.1.4.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as AESIs and reported as an SAE (Section 8.3.7), based on criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 8.3.7 (Reporting SAEs). For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by:

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

8.3.1.4.2. Myocarditis and/or Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (Section 8.3.1.2).

The Investigator's medical judgment must be applied when assessing participants reporting symptoms concerning for myocarditis and/or pericarditis contained within the CDC case definition. Diagnostic evaluation (eg, ECG, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition (Table 6) should promptly be obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be considered in those with positive test results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated. The Investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis and/or pericarditis will continue to be followed in the study for safety as per the protocol.

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical studies per the CEAC charter, to determine if they meet CDC criteria for "probable" or "confirmed" events. The CDC Working Case Definitions are provided in Section 10.4 as guidance and the CEAC is described in Section 10.1.6.

8.3.1.5. Solicited Adverse Reactions

Solicited adverse reactions will not be collected in this study.

8.3.2. Time Period and Frequency for Collecting of Safety Information

All SAEs will be collected from the signing of the ICF until EoS at the timepoints specified in the SoA (Section 1.3). All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 8.3.7. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

All AEs leading to discontinuation will be collected from the signing of the ICF until the EoS at the timepoints specified in the SoA (Section 1.3).

All AESIs will be collected from the signing of the ICF until EoS at the timepoints specified in the SoA (Section 1.3).

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

8.3.3. Method of Detecting AEs and SAEs

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

8.3.4. AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.3.5. Assessment of Severity (or Intensity) and Causality

The Investigator will make an assessment of severity (or intensity) for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild:**
  A type of AE that is usually transient and may require only minimal treatment or

therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Moderate:**
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:**
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality:

The Investigator is obligated to assess the relationship between study intervention and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

- **Not related:** There is not a reasonable possibility of a relationship to the study intervention. Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention.
- **Related:** There is a reasonable possibility of a relationship to the study intervention. There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.3.6. Follow-up of AEs and SAEs

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

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.3.7. Reporting of SAEs/AESIs

Note: AESIs will be reported to the Sponsor in the same manner and time frame as SAEs.

SAE Reporting to the Sponsor via an Electronic Data Collection Tool:

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool (ie, EDC).
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours of becoming aware of the event.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper form (see next section).

SAE Reporting to the Sponsor via Paper Data Collection Tool:

- Initial notification via email does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.
- SAE reports should be emailed to the email address provided in Section 10.2.1.

8.3.8. Regulatory Reporting Requirements for SAEs

- Prompt notification within 24 hours by the Investigator to the Sponsor of an SAE, including those considered to be a SUSAR, is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

For example, ICSRs that are required to be submitted to the European Union are submitted via the EVCTM Gateway.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- For expedited reporting purposes, the expectedness of SAEs will be assessed against the investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB for IMP(s) and comparators will be considered unexpected.

8.3.9. Pregnancy

- Any participant who becomes pregnant while participating in the study may continue study participation.
- Details of all pregnancies in participants will be collected after the start of study intervention and until 12 months after the baby's birth.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the participant's pregnancy. See Section 10.2.2.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 8.3.7).
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.7. While the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The Sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and their offspring.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

9.1. Blinding and Responsibility for Analyses

This study is observer-blind. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IMP administered until study end.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the IMP in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe may be used for injection that will maintain the blind at the time of injection. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

The study Data Blinding Plan provides details of the blinding/unblinding process and personnel. The study site staff, Investigators, study monitors, and participants will remain blinded until the EoS.

9.2. Statistical Hypothesis

There is no hypothesis testing in this study.

9.3. Analysis Sets

The analysis sets are defined in Table 5.

Table 5: Analysis Sets

Analysis Set	Description
FAS	All participants who received IMP.
Immunogenicity Subset	Participants in the FAS who have immunogenicity testing.
PPIS	The PP Immunogenicity includes participants who received planned doses of study injection per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. The PPIS will be the primary immunogenicity analysis set.
PP Set for Immunogenicity –	Participants in the PPIS who have no serologic or virologic evidence of SARS-CoV-2 infection at

Analysis Set	Description
SARS-CoV-2 negative (PPIS-Neg)	baseline, ie, who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid.
Safety Set	All enrolled participants who received IMP. The Safety Set will be used for all analyses of safety.

Abbreviations: bAb = binding antibody; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; IMP = investigational medicinal product; PP = Per-protocol; PPIS = Per-protocol Immunogenicity Subset; RT-PCR = reverse transcriptase polymer chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

9.4. Statistical Analyses

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

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Efficacy analyses based on the incidence of SARS-CoV-2 disease are not evaluated in this study.

9.4.2. Safety Analyses

All safety analyses will be based on the Safety Set. Safety will be assessed by clinical review of all relevant parameters, including SAEs, AESIs, AEs leading to withdrawal, vital sign measurements, and physical examination findings.

SAEs, AESIs and AEs leading to withdrawal will be coded by system organ class and preferred term according to the MedDRA. The number and percentage of participants with SAEs, AESIs, and AEs leading to withdrawal will be summarized, and will be presented by MedDRA system organ class and preferred term.

The number of events of SAEs, AEs leading to withdrawal, and AESIs will be reported in summary tables accordingly using descriptive statistics. Pregnancy outcomes will be listed if data warrants.

9.4.3. Immunogenicity Analyses

The immunogenicity analyses will be performed in the PPIS. Sensitivity analyses based on PPIS-Neg may be performed.

The GM level of specific nAb with corresponding 95% CI will be provided at each timepoint. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will also be provided for nAb value at each timepoint: the number of subjects (n), median, minimum and maximum.

The GMR of specific nAb with 95% CI in the Investigational mRNA-1273.815 treatment group to the licensed Spikevax treatment group at Day 15 will be computed based on the t-distribution of mean difference using the log-transformed values and then back transformed to the original scale.

GMFR of specific nAb levels with corresponding 95% CI will be provided at each timepoint over baseline level. The GMFR and 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided for fold-rise at each timepoint: the number of subjects (n), median, minimum, and maximum.

The SRR from baseline with 95% CI (using Clopper-Pearson method) will be summarized at each post-baseline timepoint. Seroresponse is defined as nAb value change from baseline (preinjection) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

9.4.4. Exploratory Analyses

There is no exploratory objective in this study.

9.4.5. Estimands

Estimands are not evaluated in this study.

9.4.6. Subgroup Analyses

Immunogenicity will be assessed in the following subgroups:

- Age (18 to <65, and ≥65 years)
- Sex (female, male)
- Baseline/preinjection SARS-CoV-2 status (negative, positive)
- Race
- Ethnicity
- Number of prior doses of COVID-19 vaccines

Safety may be assessed for the same subgroups.

9.5. Multiplicity

Multiplicity adjustment is not implemented in this study.

9.6. Sample Size Determination

A minimum of 200 participants will be randomized in a 1:1 ratio to the 2 treatment groups in this study.

9.7. Planned Analyses

9.7.1. Final Analyses

The final analysis of all applicable endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings. Details about all study analyses will be provided in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 Annex 1, Section D, No. 17, letter for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that documented informed consent was obtained before the participant was enrolled in the study and the date the documented consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

10.1.4. Recruitment Strategy

Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB/IEC.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members (if applicable), and by inspectors from regulatory authorities.
- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect

such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

No safety monitoring committee or data safety monitoring board is planned for this study.

The CRO's medical monitor, the Sponsor's medical monitor, safety and pharmacovigilance team, and the individual study site Investigators will monitor safety throughout the study. The study safety team will conduct ongoing safety reviews during the study and will be responsible for safety surveillance during the study as described in the Safety Management Plan.

An independent CEAC of medically qualified personnel, including cardiologists, will review all suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events which are reported in ongoing interventional clinical trials per the CEAC charter. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

10.1.7. Dissemination of Clinical Study Data

The Sponsor shares the information about clinical trials and results on publicly accessible sites (which may include clinicaltrials.gov, euclinicaltrials.eu, and/or other national registries), based on international and local regulatory requirements, and other clinical study disclosure commitments.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the monitoring plan.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

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

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Declaration.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment:

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

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

Study/Site Termination:

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Safety Appendix

10.2.1. SAE Reports

When EDC is unavailable, SAE reports should be emailed to drugsafety@modernatx.com.

10.2.2. Pregnancy Forms

Pregnancy forms should be emailed to drugsafety@modernatx.com.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Definitions

Person of Childbearing Potential (POCBP):

Participants who can become pregnant in the following categories are considered POCBP (fertile):

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

   - If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Person of Nonchildbearing Potential (PONCBP):

Participants in the following categories are considered PONCBP:

1. Premenopausal participant with permanent infertility due to one of the following:
   a. Documented hysterectomy.
   b. Documented bilateral salpingectomy.

c. Documented bilateral oophorectomy.

d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal participant

a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

– A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

– Participants on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
– injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from reproductive sexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

10.4. Appendix 4: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 6 as guidance.

Table 6: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

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

<table>
<tr><th>Condition</th><th colspan="2">Definition</th></tr>
<tr><td rowspan="2">Acute pericarditis[d]</td><td colspan="2">Presence of ≥2 new or worsening of the following clinical features:
• Acute chest pain[e]
• Pericardial rub on exam
• New ST-elevation or PR-depression on EKG
• New or worsening pericardial effusion on echocardiogram or MRI</td></tr>
<tr><td>OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:
• Irritability
• Vomiting
• Poor feeding
• Tachypnea
• Lethargy</td><td>OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:
• Irritability
• Vomiting
• Poor feeding
• Tachypnea
• Lethargy</td></tr>
<tr><td>Myopericarditis</td><td colspan="2">This term may be used for participants who meet criteria for both myocarditis and pericarditis.</td></tr>
</table>

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

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

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

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

c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

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

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

Reference: (Gargano et al 2021).

10.5. Appendix 5: Protocol Amendment History

CCI

[redacted]

CCI

[redacted]

CCI

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[redacted]

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