CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 4, Randomized, Observer-blind, Placebo-controlled, Crossover Study to Assess Cardiac Troponin Levels after mRNA-1273.712 Vaccine in Participants 12 through 30 years of Age
Protocol Number:	mRNA-1273-P404
Compound:	mRNA-1273.712
Brief Title:	A study to investigate cardiac troponin levels after mRNA-1273.712 vaccine in participants 12 through 30 years of age
Study Phase:	4
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	325 Binney Street Cambridge, MA 02142
Date	16 Jul 2024

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 4, Randomized, Observer-blind, Placebo-controlled, Crossover Study to Assess Cardiac Troponin Levels after mRNA-1273.712 Vaccine in Participants 12 through 30 years of Age" dated 16 Jul 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 intervention only to participants under my personal supervision or the supervision of a Subinvestigator. I will not supply study intervention 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	

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BMI	body mass index
CDC	Center for Disease Control
CEAC	cardiac event adjudication committee
CFR	Code of Federal Regulations
CI	confidence interval
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
cTnI	cardiac troponin I
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
eDiary	electronic diary
ECG/EKG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ES	evaluable set
EVCTM	EudraVigilance clinical trial module
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
hs-cTnI	high-sensitivity cardiac troponin I
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IRB	Institutional Review Board
IRT	interactive response technology
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
POCBP	person of childbearing potential
PONCBP	person of nonchildbearing potential
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	a custom-manufactured, ionizable lipid
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse event
CCI	
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 4, Randomized, Observer-blind, Placebo-controlled, Crossover Study to Assess Cardiac Troponin Levels after mRNA-1273.712 Vaccine in Participants 12 through 30 years of Age.

Brief Title:

A study to investigate cardiac troponin levels after mRNA-1273.712 vaccine in participants 12 through 30 years of age.

Rationale:

Worldwide approvals or authorizations have been issued for mRNA-1273 and variant-containing formulations across age groups at age-appropriate doses as an active immunization to prevent COVID-19. Myocarditis can occur due to SARS-CoV-2 infection. Postauthorization safety data have identified myocarditis as a very rare safety event following COVID-19 vaccination. Serum biomarkers of cardiac injury, such as cTnI, have been used clinically for suspected myocarditis cases to provide evidence of cell degradation and to help identify damage within cardiac tissue such as necrosis associated with myocarditis. While cTnI has been used as a biomarker for suspected myocarditis cases, elevated cTnI levels are not present in all cases of myocarditis, and an elevation in cTnI levels is not specific for myocarditis. To date, sufficient data are not available to describe the proportion of cTnI elevations in individuals vaccinated with mRNA-1273 or its variant-containing formulations. This Phase 4 randomized, placebo-controlled, crossover study will assess cTnI levels after vaccination with mRNA-1273.712 or placebo in individuals 12 through 30 years of age. This study design will allow comparison of cTnI elevation after mRNA-1273.712 vaccination versus no vaccination.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• Proportion of participants with elevated cTnI level at Day 4 or Day 32 (3 days after Injection 1 or Injection 2).
Secondary	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• Proportion of participants with elevated cTnI level at Day 1 (baseline). • Proportion of participants with elevated cTnI level at Day 29 or Day 57 (28 days after Injection 1 or Injection 2).
• To evaluate the safety of mRNA-1273.712.	• SAEs, MAAEs, AESIs, and AEs leading to withdrawal throughout study.

Objectives	Endpoints
Exploratory	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• cTnI levels at Day 1, Day 4, Day 29, Day 32, and Day 57.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; cTnI = cardiac troponin I; MAAE = medically attended adverse event; SAE = serious adverse event

Overall Design Synopsis:

This is a Phase 4 study designed as a randomized, observer-blind, placebo-controlled, crossover clinical study to assess cTnI levels after vaccination with the KP.2 variant-containing mRNA-1273.712 COVID-19 vaccine in individuals 12 through 30 years of age. The study will be conducted at clinical study sites across the United States.

The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until EOS. Unblinded pharmacy personnel (of limited number) will be assigned to study intervention accountability procedures and will prepare and administer mRNA-1273.712 or placebo to all participants. Unblinded study site monitors, not involved with other aspects of monitoring, will be assigned as the study intervention accountability monitors.

Participants will receive study intervention by IM injection on Day 1. The study will follow a crossover design and the study intervention sequence will be switched on Day 29. Participants will be followed for approximately 1 month after each injection, for a total study duration of approximately 2 months. Safety assessments throughout the study will include SAEs, MAAEs, AESIs, and AEs leading to withdrawal.

Blood samples will be collected from all participants at preinjection on the day of each injection, as well as at 3 and 28 days after each injection for assessment of cTnI. To aid interpretation of cTnI assessment, participants will record vigorous physical activities in their eDiary for specific periods during the study (ie, if an elevated cTnI level is detected during the analysis, the activity data for that participant will be reviewed for correlation of vigorous physical activities with elevated cTnI levels) (Table 2). Depending on when the study injections or EOS is scheduled to be completed, the participant must complete the eDiary for 4 consecutive days post-Injection 1 (Day 1), 4 consecutive days pre- and post-Injection 2 (Day 29), and 4 consecutive days prior to EOS visit (Day 57), and on the day of the EOS visit. Participants will be encouraged, but not required, to avoid vigorous physical activities, when possible, for 4 days before and after each study injection.

- Note: Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

The study will be comprised of 5 scheduled in-clinic visits including a combined Screening and Day 1 Visit. Procedures for Screening and injection/baseline should be performed on the same day (Day 1 Visit) but may be performed on 2 separate days if needed due to extenuating circumstances (Section 1.3). This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

Study Duration:

Participants will be in the study for approximately 2 months, which includes:

- Up to 7 days for Screening and Baseline (Day -7 to Day 1)
- Administration of study injection (Day 1 and Day 29) and
- Approximately 2 months of follow-up (28 days after each injection)

Number of Participants:

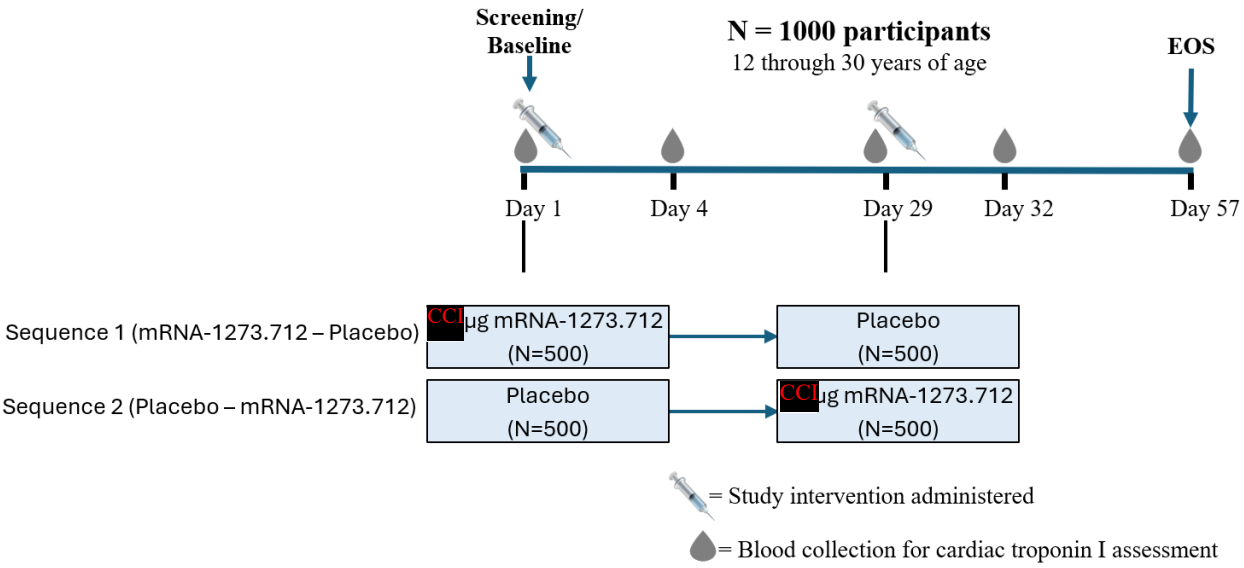
Approximately 1000 adolescent and adult (12 through 30 years of age, inclusive) participants will be randomized in a 1:1 ratio (approximately 500 participants in each intervention sequence) to receive either CCI µg of mRNA-1273.712 followed by placebo 28 days later (mRNA-1273.712 – placebo [Sequence 1]) or placebo followed by CCI µg of mRNA-1273.712 28 days later (placebo – mRNA-1273.712 [Sequence 2]). The interval between the 2 study injections is not expected to introduce any carry-over effects given that troponin elevations are expected to persist for a few days to a couple of weeks, depending on the underlying cause. At least 45% of participants will be enrolled in each of the age groups (12 through 17 years and ≥18 through 30 years) at clinical study sites across the US.

Study Interventions:

A CCI-µg dose of mRNA-1273.712 and placebo, administered IM, in a crossover manner (Figure 1).

1.2. Schema

Figure 1: Study Design



Abbreviation: EOS = end of study

1.3. Schedule of Activities

Table 1: Schedule of Activities

Visit Number	**1**	**2**	**3**	**4**	**5**
Type of Visit	**C**	**C**	**C**	**C**	**C/EOS**
Month Timepoint	**M0**		**M1**		**M2**
Timepoint	**D1[a] (Screening and Baseline)**	**D4**	**D29**	**D32[b]**	**D57[b]**
Window Allowance (Days)	**-7**	**-2**	**+3**	**-2**	**±3**
Days Since Injection	0	3	28/0	3	28
ICF, demographics, concomitant medications, medical history	X				
Confirm participant meets inclusion/exclusion criteria	X				
Full physical examination[c]	X				
Vital sign measurements[d]	X	X	X	X	X
Pregnancy testing[e]	X		X		
Study injection (including 15-minute postinjection observation period)[f]	X		X		
Blood collection for cardiac troponin I assessment[g]	X	X	X	X	X
Recording of SAEs, MAAEs, AESIs, AEs leading to withdrawal[h]	X	X	X	X	X
Recording of concomitant medications[i]	X	X	X	X	X
Recording of nonstudy vaccinations	X	X	X	X	X
Review of eDiary[j]	X	X	X	X	X
Study completion					X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = clinic visit; D = day; eDiary = electronic diary; EOS = end of study; ICF = informed consent form; M = month; MAAE = medically attended adverse event; SAE = serious adverse event.

a. The Screening Visit and Day 1 (injection/baseline) visit should be performed on the same day. If because of extenuating circumstances, Screening and Day 1 visits need to be performed on 2 different days, completion of Informed Consent Form, demographics, concomitant medications, medical history and confirming participant meets inclusion/exclusion criteria must be completed on the same day (Screening), and the remaining study procedures must be done on the same day as the injection (Day 1).

b. Visit 4 must be scheduled 3 days after Visit 3 (a window of up to -2 days is permitted). EOS Visit must be scheduled 28 days after Visit 3 (a 3-day window is permitted).

c. 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.

d. On the day of injection (Day 1 and Day 29), vital signs are to be collected before and after injection.

e. Pregnancy tests are to be collected before each injection (Section 8.2.6).

f. 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 study intervention at the discretion of the Investigator. Participants will be encouraged but not required to avoid vigorous physical activities 4 days before and after each injection.

g. For the blood collection on Day 1 and Day 29, blood will be drawn prior to study injection.

h. 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.

i. Concomitant medications (associated with SAEs, MAAEs, AESIs, or AEs leading to withdrawal) and non-study vaccinations will be recorded through the EOS.
j. Study site staff will review eDiary data with participants at each clinic visit after the first injection.

Table 2: Schedule of eDiary Collection of Vigorous Physical Exercise

Visit Number	**1**				**2**				**3**				**4**				**5**
Description	**4 days post-Injection #1**				**4 days pre-Injection #2**				**4 days post-Injection #2**				**4 days pre-EOS**				**EOS[b]**
Day[a]	1	2	3	4	25	26	27	28	29	30	31	32	53	54	55	56	57

Abbreviations: eDiary = electronic diary; EOS = end of study.
a. Window Allowance (Days) for the study injections and EOS are presented in Schedule of Activities (Table 1). Depending on when the study injections or EOS is completed, the participant must complete the eDiary for: 4 consecutive days post-Injection 1, 4 consecutive days pre- and post-Injection 2, 4 consecutive days prior to EOS visit, and on the day of the EOS visit.
b. eDiary entry will be logged at clinic visit on Day 57.

2. INTRODUCTION

Worldwide approvals or authorizations have been issued for mRNA-1273 and variant-containing formulations across age groups at age-appropriate doses as an active immunization to prevent COVID-19.

2.1. Study Rationale

Myocarditis can occur due to SARS-CoV-2 infection. Postauthorization safety data have identified myocarditis as a very rare safety event following COVID-19 vaccination. Serum biomarkers of cardiac injury, such as cTnI, have been used clinically for suspected myocarditis cases (Wu 2017, Bozkurt et al 2016), to provide evidence of cell degradation and to help identify damage within cardiac tissue such as necrosis associated with myocarditis (Wu 2017, Goldmann et al 2001). However elevated cTnI levels are not present in all cases of myocarditis and are not specific for myocarditis. Cardiac troponin I levels may also be elevated with other cardiac and noncardiac conditions including strenuous exercise, rhabdomyolysis, and autoimmunity (McCarthy et al 2019, Wu 2017, Goldmann et al 2001). To date, sufficient data are not available to describe the proportion of cTnI elevations in individuals vaccinated with mRNA-1273 or its variant-containing formulations.

This Phase 4 randomized, placebo-controlled, crossover study will assess cardiac troponin I levels after vaccination with mRNA-1273.712 or placebo in individuals 12 through 30 years of age. This study design will allow comparison of cardiac troponin I elevation after mRNA-1273.712 vaccination versus no vaccination.

2.2. Background

Myocarditis and/or pericarditis are very rare events, which have been observed more often after the second dose compared to the first dose and less often after subsequent doses. Most cases of myocarditis are generally mild and self-limiting. Onset has primarily occurred within 7 days after vaccination.

One study (Albertson et al 2024) evaluated the proportion of cTnI elevations in participants who received BNT162b2 COVID-19 vaccine and placebo. Among 5- to <30-year-olds, cTnI levels were rarely elevated (<1.0%) and generally similar before and after vaccination. The cTnI levels were also similar between BNT162b2 and placebo recipients by age (in 5 to <30 years, 12 to 30 years, and 5 to 11 years).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mRNA-1273 and its 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. The rate of anaphylaxis has been reported as 1.31 (95% CI: 0.90-1.84) per million vaccine doses administered (McNeil et al 2016). As a precaution, all participants will remain under observation at the study site for at least 15 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 vaccine 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 injection site pain, erythema (redness), or swelling/induration (hardness) at the injection site and/or axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

Systemic ARs may also occur after vaccination, the majority of which are mild to moderate in severity. Systemic ARs 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 8.3.1.5.2) 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).

2.3.2. Benefit Assessment

The following benefits may occur to participants:

- mRNA-1273.712 COVID-19 vaccine may be effective against COVID-19 including disease caused by variants of concern.
- Participant safety will be monitored throughout the study.

2.3.3. Overall Benefit/Risk Conclusion

All participants will receive the KP.2 variant-containing mRNA-1273.712 and safety will be monitored throughout the study.

Taking into account the participants' risk of COVID-19, and the clinical data to date, the Sponsor considers the anticipated benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are described in Table 3.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• Proportion of participants with elevated cTnI level at Day 4 or Day 32 (3 days after Injection 1 or Injection 2).
Secondary	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• Proportion of participants with elevated cTnI level at Day 1 (baseline). • Proportion of participants with elevated cTnI level at Day 29 or Day 57 (28 days after Injection 1 or Injection 2).
• To evaluate the safety of mRNA-1273.712.	• SAEs, MAAEs, AESIs, and AEs leading to withdrawal throughout study.
Exploratory	
• To assess cTnI values in participants who received mRNA-1273.712 or placebo.	• cTnI levels at Day 1, Day 4, Day 29, Day 32, and Day 57.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; cTnI = cardiac troponin I; MAAE = medically attended adverse event; SAE = serious adverse event.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4 study designed as a randomized, observer-blind, placebo-controlled, crossover clinical study to assess cTnI levels after vaccination with the KP.2 variant-containing mRNA-1273.712 COVID-19 vaccine in individuals 12 through 30 years of age.

The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until study end. Unblinded pharmacy personnel (of limited number) will be assigned to study intervention accountability procedures and will prepare and administer mRNA-1273.712 or placebo to all participants. Unblinded study site monitors, not involved with other aspects of monitoring, will be assigned as the study intervention accountability monitors.

Approximately 1000 adolescent and young adult participants (12 through 30 years of age, inclusive, at Screening) will be enrolled and randomized in a 1:1 ratio (approximately 500 participants in each intervention sequence) to receive 2 study interventions (mRNA-1273.712 and placebo), in a crossover design. After each study intervention, the participant will be followed for 28 days. Participants will receive either mRNA-1273.712 CCI µg followed by placebo 28 days later (Sequence 1) or placebo followed by mRNA-1273.712 CCI µg 28 days later (Sequence 2). The interval between the study injections is not expected to introduce any carry-over effects given that troponin elevations are expected to persist for a few days to a couple of weeks, depending on the underlying cause. At least 45% of participants will be enrolled in each of the age groups (12 through 17 years and ≥18 through 30 years).

Participants will be followed for approximately 1 month after each study injection, for a total duration of approximately 2 months overall. Safety assessments throughout the study will include SAEs, MAAEs, AESIs, and AEs leading to withdrawal.

Blood samples will be collected from participants on scheduled visits (at injection visits, samples will be collected prior to injection) as specified in the SoA (Table 1) for assessment of cTnI. To aid in interpretation of cTnI assessment, participants will record vigorous physical activities in an eDiary for specific periods during the study (ie, if an elevated cTnI level is detected during the analysis, the activity data for that participant will be reviewed for correlation of vigorous physical activities with elevated cTnI levels) (Table 2). Depending on when the study injections or EOS is scheduled to be completed, the participant must complete the eDiary for 4 consecutive days post-Injection 1 (Day 1), 4 consecutive days pre- and post-Injection 2 (Day 29) , and 4 consecutive days prior to the EOS visit (Day 57), and on the day of the EOS visit. Participants will be encouraged, but not required, to avoid vigorous physical activities, when possible, for 4 days before and after each study injection.

- Note: Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

The study will be comprised of 5 scheduled in-clinic visits including a combined Screening and Day 1 Visit. Procedures for Screening and injection/baseline should be performed on the same day (Day 1 Visit) but may be performed on 2 separate days if needed due to extenuating circumstances (Section 1.3). This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

Participants will be in the study for approximately 2 months, which includes up to 7 days for Screening and Baseline (Day -7 to Day 1), with administration of study injection on Day 1 and Day 29 and approximately 2 months of follow-up (28 days after each injection).

4.2. Scientific Rationale for Study Design

This Phase 4 randomized, placebo-controlled, crossover study will assess cTnI levels after vaccination with mRNA-1273.712 or placebo in individuals 12 through 30 years of age. This study design will allow comparison of cTnI elevation after an mRNA-1273.712 vaccination versus no vaccination. The crossover design will provide all participants the benefits of receiving the updated KP.2 variant-containing COVID-19 vaccine.

4.3. Justification for Dose

The [redacted] µg dose level is the currently licensed dose for Spikevax® (Moderna's COVID-19 vaccine).

4.4. End of Study Definition

The end of the study is defined as the date that the analyses are completed for the primary and secondary endpoints for the study globally.

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 procedure shown in the SoA (Table 1).

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. At least 12 through 30 years of age, inclusive, at the time of signing the informed consent (Screening Visit).
2. Investigator's assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
4. Assigned female at birth and/or assigned male at birth.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   - Participants who could become pregnant:
     - A participant who could become pregnant is eligible to participate if they are not pregnant or breast/chestfeeding and one of the following conditions applies:
     - Is a PONCBP as defined in Appendix 4 Contraceptive and Barrier Guidance.

     OR

     - Is a POCBP and fulfills all of the following criteria:

       a. Has a negative highly sensitive pregnancy test on the day of injection prior to injection (Day 1)

       b. Has been using a highly effective or effective contraceptive method as described in Appendix 4 Contraceptive and Barrier Guidance or has abstained from all activities that could lead to pregnancy for at least 28 days prior to the first injection (Day 1). The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first injection.

       c. Has agreed to continue adequate contraception through EOS.
   - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.6.
   - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

5.2. Exclusion Criteria

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

1. History of anaphylaxis or severe hypersensitivity reaction requiring medical intervention after receipt of any mRNA vaccine or therapeutic or any components of an mRNA vaccine or therapeutic.
2. Has known history of SARS-CoV-2 infection within 3 months prior to enrollment.
3. Has a documented history of myocarditis or pericarditis.
4. 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 within the visit window and will retain their initially assigned participant number.
5. Has known conditions that may cause elevated cTnI.
   - Cardiac disease/conditions including rhythm disorders and congenital heart disease
   - Diabetes
   - Uncontrolled hypertension (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg)
   - Alcohol or substance abuse
   - Kidney disease
   - Severe obesity, defined as BMI ≥40 kg/m^2 (>20 years) or severe obesity defined as BMI for sex and age ≥120% of the 95th percentile [BMI ≥35 kg/m^2] (for 12 to 20 years) (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm)
   - Other conditions – see complete list in Appendix 6
6. 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.
7. 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.
8. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections disease.
9. History of Guillain-Barré syndrome.
10. Coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.

11. History of malignancy within previous 5 years (excluding nonmelanoma skin cancer).
12. Receipt of the following:
    - COVID-19 vaccine within 3 months prior to the first injection or if planning to receive at any time during the study (except for study intervention).
    - Any other licensed vaccine within 28 days before the study injection or planned receipt prior to EOS.
    - 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.
    - Systemic immunoglobulins or blood products within 3 months prior to the Screening/Baseline Visit or plans for receipt during the study.
13. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
14. Has participated in an interventional clinical study within 28 days prior to the Screening visit or plans to participate in an interventional clinical study of an investigational vaccine or drug while participating in this study.
15. 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 assigned to study intervention/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 not be rescreened.

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Body temperature (oral) must be measured on injection visits before study injection is administered. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for injection, the participant may receive the study injection at a later date within the time window specified in the relevant SoA (Table 1), or the participant may be discontinued from study intervention at the discretion of the Investigator (Section 7.2):

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

Participants with a minor illness without fever, as assessed by the Investigator, can be administered study intervention. 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 study injection 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.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and non-investigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Interventions Administered

Participants will receive mRNA-1273.712 and placebo in the study using a crossover design (Table 4). The mRNA-1273.712 is an mRNA-LNP dispersion consisting of mRNA encoding the S-2P of the SARS-CoV-2 KP.2 subvariant of Omicron, formulated in a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

Each participant will be administered a CCI µg dose of mRNA-1273.712 and placebo in a crossover design:

- mRNA-1273.712 – placebo sequence: CCI µg of mRNA-1273.712 followed by placebo 28 days later (Sequence 1)
- Placebo – mRNA-1273.712 sequence: placebo followed by CCI µg of mRNA-1273.712 28 days later (Sequence 2)

Table 4: Study Interventions Administered

Intervention Name	mRNA-1273.712	Placebo
Dose	CCI µg	N/A
Dosage Form	Dispersion for injection	Sodium chloride for injection
Route of Administration	IM injection	IM injection

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid; N/A = not applicable.

Study Intervention Packaging and Labeling

The study interventions used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH Guidance for Industry, GCP guidelines, guidelines for Quality System Regulations, and applicable regulations. For more information on study intervention packaging and labeling, please refer to the pharmacy manual.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Preparation of Study Intervention for Injection

The study sites will be appropriately staffed with an unblinded pharmacist who will prepare the study intervention, will administer the study intervention to participants, and will store the study interventions. For more details on preparation of study intervention, please refer to the mRNA-1273-P404 Pharmacy Manual.

6.2.2. Administration of Study Intervention

Each participant will receive study intervention by IM injection on Day 1 and Day 29 according to their assigned sequence (see SoA, Table 1) and according to the procedures specified in the mRNA-1273-P404 Pharmacy Manual.

At each visit when study intervention is administered, participants will be monitored for a minimum of 15 minutes after administration. Assessments will include vital sign measurements and monitoring for any SAE, MAAE, AESI, or AE leading to withdrawal (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 Intervention Delivery and Receipt

Instructions for study intervention delivery and receipt are described in the mRNA-1273-P404 Pharmacy Manual.

6.2.4. Study Intervention Storage

For details on study intervention storage, please refer to the mRNA-1273-P404 Pharmacy Manual.

6.2.5. Study Intervention Accountability

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

Additional details are provided in the mRNA-1273-P404 Pharmacy Manual.

6.2.6. Study Intervention Handling and Disposal

A study site monitor will review the inventory and accountability log during study site visits and at the completion of the study. Once fully reconciled at the study site at the end of the study and approved by the Sponsor, the study interventions will be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Study interventions 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 IRT, 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 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. In the event of a medical emergency requiring identification of the study intervention 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. 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 study intervention accountability procedures and will prepare and administer mRNA-1273.712 or placebo to all participants. These pharmacy personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of study intervention 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 study intervention accountability monitors. They will have responsibilities to ensure that study sites are following all proper study intervention accountability, preparation, and administration procedures.

6.5. Study Intervention Compliance

When participants are given the study injection, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each study injection administered will be recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of injection by a member of the study site team other than the person administering the study intervention. If a participant does not receive study intervention, the reason for the missed injection will be recorded.

6.6. Dose Modification

No dose modification is permitted for this study. Criteria for delaying or discontinuing study intervention administration are provided in Section 6.9.3.

6.7. Continued Access to Study Intervention After the EOS

There is no planned intervention after the end of the study.

6.8. Treatment of Overdose

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

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

- Provide or arrange for medical or supportive care as needed.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose.
- All instances of overdose must be reported by the Investigator to the Sponsor within 24 hours and reported to the IRB per local guidelines, as applicable.
- Any AE associated with the overdose of the study intervention must be reported if they meet the protocol criteria for reporting (SAE, MAAE, AESI, or AE leading to withdrawal).

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. All previous COVID-19 vaccinations received prior to informed consent/assent will be recorded. The following information about prior medications needs to be reported:

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

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

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)/legally authorized representative(s) regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations, including seasonal influenza, administered within the period starting 28 days before the first study injection through EOS.

Any concomitant medications relevant to or for the treatment of an SAE, MAAE, AESI, or AE leading to withdrawal. Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a medication listed in Section 5.2 or Section 6.9.3, the Investigator and the CRO's medical monitor will make a joint decision about continuing or withholding injection 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 Elimination of a Participant from Evaluable Set

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

- Receipt of any COVID-19 vaccine within 3 months before the first injection and any other licensed vaccine within 28 days before any study injection. If a participant receives any nonstudy COVID-19 vaccine or other licensed vaccine after the first study injection, the participant may continue study participation but may be removed from the study analyses.
- Any investigational or nonregistered product (drug or vaccine) other than the study intervention used during the study period.
- Concomitant medications considered exclusionary in Section 5.2.

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

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for cTnI levels and safety assessments. See the EOS Visit in the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The Investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from study intervention if the participant experiences any of the following prior to injection on Day 1 or Day 29:

- A POCBP 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

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). If a participant chooses to withdraw from the study, the Investigator (or designee) should document the reason for withdrawal in EDC if the participant provides one.
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1). See the EOS Visit in the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- A participant who withdraws from the study will not be replaced.
- 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.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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

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

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

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

7.3. Lost to Follow-up

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

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

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

- The site must attempt to contact the participant and reschedule the missed visit. If contact is made, the participant should be counseled 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 lost to follow-up, 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 should be documented in the participant's source documents.
- If due diligence, as described above, has been completed, the participant will be considered lost to follow-up and discontinued from the study.

7.4. Pause Rules

Not applicable for this study.

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 (Table 1).

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.

General considerations for study assessments and procedures include the following:

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study vaccination or participation in the study.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

8.1. Efficacy and/or Immunogenicity Assessments

No efficacy and/or immunogenicity assessments are planned in this study.

8.2. Safety Assessments

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

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

- AEs leading to withdrawal from injection on Day 1 through EOS.
- MAAEs from injection on Day 1 through EOS.
- AESIs from injection on Day 1 through EOS.
- SAEs from informed consent signing through EOS.
- Vital sign measurements before and after injection.
- Physical examination findings (if performed after initial exam).

- Details of all pregnancies (Section 10.3.2) in POCBP participants will be collected after the start of study intervention 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 site 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, MAAEs, AESIs, AEs leading to withdrawal, concomitant medications relevant to or for the treatment of the SAEs, MAAEs, 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

Participants will be asked to use an eDiary to collect information about strenuous physical exercise at the timepoints provided in Table 2. If an elevated cTnI level is detected during the analysis, the activity data for that participant will be reviewed for correlation of vigorous physical activities with elevated cTnI levels.

Study site staff will review eDiary data with participants at each clinic visit after the first injection.

8.2.3. Physical Examinations

- A full physical examination, including height and weight, will be performed at scheduled timepoints as indicated in the SoA (Table 1). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities.
- Symptom-directed physical examinations may be performed at other timepoints at the discretion of the Investigator. Any abnormalities should be documented.
- Body mass index will be calculated at the Screening/Baseline Visit only.

8.2.4. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse 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 (Table 1).

- 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 study intervention at the discretion of the Investigator.
- Vital signs will be assessed before and approximately 15 minutes after injection on the day of injection (Day 1 and Day 29).
- When procedures overlap and are scheduled to occur at the same timepoint, the order of procedures should be vital sign measurements and then blood collection.

8.2.5. Clinical Safety Laboratory Tests

Planned timepoints for blood collections for assessing cTnI levels are provided in the SoA (Table 1); blood samples will be collected prior to administration of study injection. Elevated cTnI levels will be defined as per the threshold described in product insert of the hs-cTnI assay kit. As this is a blinded study, the results of the hs-cTnI assay will not be available until after the study is completed, and therefore will not be shared with the participant during the study.

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

Planned timepoints for collection of highly sensitive urine hCG pregnancy test for POCBP are provided in the SoA (Table 1); samples will be collected before administration of study injection.

- Refer to Section 5.1 (Inclusion Criteria) for pregnancy testing entry criteria.
- At any time, a pregnancy test, either via blood or point-of-care urine, can be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

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

The definitions of AEs, SAEs, SUSARs, MAAEs, 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 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 AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 6.9.3). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Medication errors, pregnancies, and uses outside of the study protocol (including misuse and abuse) are being subject to the same collection/reporting rules as AEs.

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. MAAEs are defined in in Section 8.3.1.4. AESIs are defined in Section 8.3.1.5. Solicited adverse reactions will not be collected in this study.

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 preexisting 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 interactions with other vaccines.
- 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.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events not 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 preexisting 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 serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

8.3.1.4. MAAE

A MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to a study site for unscheduled assessments not required per protocol (eg, rash assessment, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (eg, emergency room, urgent care, primary care physician).

8.3.1.5. AESI

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 AESIs defined for this protocol can be found in Section 10.5.

8.3.1.5.1. 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.

8.3.1.5.2. 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 myocarditis and/or pericarditis contained within the CDC case definition.

Diagnostic evaluation (eg, ECG/EKG) and laboratory testing (eg, troponin) should be obtained promptly if considered clinically indicated in any participant with concerning signs/symptoms. Diagnostic imaging (eg, cMRI, echocardiogram) should be obtained in those with positive diagnostic or laboratory test results or clinically significant symptoms for myocarditis/ pericarditis without other identifiable causes. The participant should be referred to a cardiologist. 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 cases classification as "probable" or "confirmed" events. The CDC Working Case Definitions are provided in Section 10.5 as guidance, and the CEAC is described in Section 10.1.6.

8.3.2. Time Period and Frequency for Collecting of Safety Information

All MAAEs, AESIs, and AEs leading to withdrawal will be collected after injection on Day 1 until EOS at the timepoints specified in the SoA (Table 1). All SAEs will be collected from signing of informed consent until EOS at the timepoints specified in the SoA (Table 1). 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.

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.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs; however, if the condition worsens at any time after study intervention administration, it will be recorded and reported as an AE if it meets reporting criteria.

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 the 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 the 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 Intensity and Causality

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

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

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
  - **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/MAAEs/AESIs/AEs leading to withdrawal 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.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology (if available).
- 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/SUSARs

AESIs and SUSARs 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

- If EDC is unavailable and the site needs to use a paper form to report SAEs, email transmission of the SAE paper data collection tool may be used to transmit this information to the Sponsor.
- 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.
- AE reports should be emailed to the email address provided in Section 10.3.1.

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 towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical

investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators. For example, for reports that are required to be submitted to the European Union (ICSRs), will be 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 study treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB for study intervention will be considered unexpected.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.9. 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 28 days following the last injection. Participants who become pregnant at any time during the study should remain in the study and complete all study visits as scheduled.
- 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 10.3.2).
- 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

Pharmacokinetics parameters are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamics parameters are not evaluated in this study.

8.6. Future Genetics Research

Future genetics research will not be performed.

8.7. Biomarkers

Blood samples for assessment of cTnI levels will be collected from all participants at the following timepoints, as specified in the SoA (Table 1) and as detailed in the Laboratory Manual provided separately to the study sites.

- Baseline Day 1 (before injection)
- Day 4 (3 days after Injection 1)
- Day 29 (before injection) (28 days after Injection 1)
- Day 32 (3 days after Injection 2)
- Day 57 (28 days after Injection 2)

Elevated cTnI values will be defined based on the sex-specific 99th percentile cutoff of the assay that will be used for the study.

The Sponsor may store samples for the time period specified in the ICF to achieve study objectives. Samples may be used for further research by the Sponsor or others such as universities or other companies to contribute to the understanding of cardiac or other diseases, the development of related or new treatments, or research methods, as specified in the ICF.

8.8. Immunogenicity

Not applicable.

8.9. 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 intervention 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 study intervention administered until study end.

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 planned in this study. The proposed number of participants is considered sufficient to provide a descriptive analysis of the rates of cTnI elevations after study intervention.

9.3. Analysis Sets

The analysis sets are defined in Table 5.

Table 5: Analysis Sets

Analysis Set	Description
Randomization Set	All randomized participants.
Safety Set	All randomized participants who receive at least one dose of study intervention. Participants will be included in the intervention group corresponding to Injection 1 or Injection 2 received.
Evaluable Set	All participants in the Safety Set who have no major protocol deviations or conditions/medications that impact critical or key analysis data.

9.4. Statistical Analyses

The SAP will be 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

No efficacy endpoints are planned for this study.

9.4.2. Safety Analyses

All safety analyses will be based on the Safety Set.

Safety will include SAEs, MAAEs, AESIs, AEs leading to withdrawal, vital sign measurements, and physical examination findings.

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

The number of events of SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be reported in summary tables accordingly using descriptive statistics. Pregnancy outcomes will also be summarized.

The safety summaries will be presented by study intervention and injection (ie, post-Injection 1 and pre-Injection 2, and post-Injection 2), and for participants who receive the mRNA-1273.712 for Injection 1 or Injection 2 (ie, post-mRNA-1273.712 injection and throughout the study).

9.4.3. Biomarker Analyses

cTnI analysis

All statistical analyses will be descriptive.

The primary analysis for the proportion of cTnI elevations will be performed in the ES. The following groups are defined for the analysis of cTnI:

- mRNA-1273.712 group: participants who receive mRNA-1273.712 for Injection 1 in the mRNA-1273.712 - placebo sequence (Sequence 1), and participants who receive mRNA-1273.712 for Injection 2 in the placebo - mRNA-1273.712 sequence (Sequence 2).
- placebo group: participants who received placebo for Injection 1 in the placebo – mRNA-1273.712 sequence (Sequence 2), and participants who receive placebo for Injection 2 in the mRNA-1273.712 - placebo sequence (Sequence 1).

A participant may be included in both mRNA-1273.712 group and placebo group according to Injection 1 and Injection 2 received for the analysis of cTnI.

The primary endpoint for the proportion of participants with elevated cTnI at Day 4 or Day 32 (3 days after Injection 1 or Injection 2) will be summarized for the mRNA-1273.712 group and placebo group in the ES.

The secondary endpoints of the proportion of participants with elevated cTnI at preinjection Day 1, and the proportion with elevated cTnI at Day 29 (28 days after Injection 1 and

pre-Injection 2) or Day 57 (28 days after Injection 2) will be summarized for the mRNA-1273.712 group and placebo group in the ES.

The proportion of participants with elevated cTnI at each timepoint (Day 1, Day 4, Day 29, Day 32, and Day 57) for mRNA-1273.712 group and placebo group will be summarized for mRNA-1273.712 group and placebo group, overall, by age group (12 through 17 and ≥18 through 30 years of age) and by sex.

The proportions of participants with elevated cTnI described above will be summarized using percentage and 95% CI with the Clopper-Pearson method. The 95% CI for the difference in proportions between mRNA-1273.712 group and placebo group will be calculated using the Miettinen and Nurminen method.

9.4.4. Exploratory Analyses

The exploratory analysis for this study is to assess cTnI values in participants who received mRNA-1273.712 or placebo. Blood samples for these assessments will be collected as specified in the SoA (Table 1). Additional exploratory analyses may be described in the SAP.

9.4.5. Estimands

No estimands were defined for this study.

9.4.6. Subgroup Analyses

Subgroup analyses may be performed according to the following:

- Age (12 through 17 and ≥18 through 30 years)
- Sex (female, male) at birth
- Race
- Ethnicity

Safety may be assessed for the same subgroups.

9.5. Multiplicity

Multiplicity control is not relevant for this study.

9.6. Sample Size Determination

Approximately 1000 participants will be randomized in a 1:1 ratio to one of 2 intervention sequences (approximately 500 participants in each intervention sequence) in this study, to receive [redacted] µg of mRNA-1273.712 followed by placebo 28 days later (mRNA-1273.712 – placebo [Sequence 1]) or to receive placebo followed by [redacted] µg of mRNA-1273.712 28 days later (placebo – mRNA-1273.712 [Sequence 2]). Approximately 1000 participants will receive [redacted] µg of mRNA-1273.712 for Injection 1 or Injection 2, due to the crossover design. Assuming approximately 10% of participants would be excluded from the mRNA-1273.712 group (Injection 1 or Injection 2) in the ES due to any reasons (eg, early dropout, and major protocol deviations that impact key analysis data), the study has more than 90% probability to observe at

least 1 participant receiving mRNA-1273.712 (Injection 1 or Injection 2) with an elevated cTnI at a true rate of 0.3%.

9.7. Planned Analyses

No interim analysis is planned for this study. 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. Additional information on the 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 Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's brochure, 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 Subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives 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 or their legally authorized representative.

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 de-identified 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 studies 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 studies 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.
- 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, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the

test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

- Source documents 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 CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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: Adverse Event of Special Interest

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

Table 6 describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. However, this is not a comprehensive list of terms. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per protocol, even when they occur during/following COVID infection.

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

Table 6: Adverse Events of Special Interest

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

Medical Concept	Additional Notes
	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.
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).

Medical Concept	Additional Notes
	• 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.

10.3. Appendix 3: Safety Appendix

10.3.1. SAE Reports

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

10.3.2. Pregnancy Forms

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. 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 injection 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.

10.4.2. 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 – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – Oral – Injectable

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
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.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. a. Contraceptive 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. d. Considered effective, but not highly effective - failure rate of ≥1% per year.

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

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 7 as guidance.

Table 7: 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)

Condition	Definition	
	AND • No other identifiable cause of the symptoms and findings	**AND** • No other identifiable cause of the symptoms and findings
Acute pericarditis[d]	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	
	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
Myopericarditis	This term may be used for participants who meet criteria for both myocarditis and pericarditis.	

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

Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events, (Gargano et al 2021). 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).

10.6. Appendix 6: Exclusion Criterion 6 – Other Conditions That May Cause Elevated Cardiac Troponin I Levels

In addition to the conditions listed in exclusion criterion #5 (Section 5.2), other medical conditions that may cause elevated cTnI levels are listed in Table 8.

Table 8: Other Conditions That May Cause Elevated Cardiac Troponin I Levels

Infiltrative diseases	• Amyloidosis • Sarcoidosis • Hemochromatosis
Respiratory	• Chronic lung disease • Pulmonary embolism with right ventricular dysfunction
Inherited diseases	• Duchenne muscular dystrophy
Myocardial injury or trauma (within 1 month of Screening)	• Cardiac surgery • Chest wall trauma • Drug toxicity (eg, adriamycin, 5-fluorouracil)
Autoimmune diseases	• Autoimmune diseases that can cause inflammation or direct damage to the heart – Systemic lupus erythematosus – Rheumatoid arthritis – Scleroderma – Sarcoidosis – Polyarteritis nodosa
Miscellaneous	• Rhabdomyolysis (within 1 month of screening)

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