ModernaTX, Inc.

Protocol mRNA-1273-P404

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

Statistical Analysis Plan

Version 1.0
Version Date of SAP: 18FEB2025

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Document History

Version	Date	Description of main modifications
1.0	18 February 2025	Original version per the study protocol dated on 16JUL2024.

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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
CI	Confidence Interval
CMQ	Customized MedDRA Query
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
cTnI	Cardiac Troponin I
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOS	End of Study
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
hs-cTnI	High-Sensitivity Cardiac Troponin I
ICF	Informed Consent Form
IM	Intramuscular(ly)
IP	Investigational Product
IRT	Interactive Response Technology
MAAE	Medically Attended Adverse Event
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mRNA	Messenger Ribonucleic Acid
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Definition
SMQ	Standardized MedDRA Query
SoA	Schedule of Activities
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P404, is based on the most recent approved clinical study protocol (CSP), dated 16-JUL-2024 and case report form (CRF) dated 30-SEP-2024.

This Phase 4 randomized, placebo-controlled, crossover study will assess cardiac troponin I (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 cardiac troponin I elevation after mRNA-1273.712 vaccination versus no vaccination.

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

In this document, intervention, injection, and dose are used interchangeably.

2. Study Objectives

2.1 Primary Objective

To assess cTnI values in participants who received mRNA1273.712 or placebo at Day 4 or Day 32 (3 days after Dose 1 or Dose 2)

2.2 Secondary Objectives

- To assess cTnI values in participants who received mRNA1273.712 or placebo at Day 1, Day 29, or Day 57.
- To evaluate the safety of mRNA1273.712 throughout study.

2.3 Exploratory Objective

To assess cTnI values in participants who received mRNA-1273.712 or placebo.

3. Study Endpoints

3.1 Primary Endpoint

Proportion of participants with elevated cTnI level at Day 4 or Day 32 (3 days after Injection 1 or Injection 2).

3.2 Secondary Endpoints

- 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).
- Serious adverse events (SAEs), medically-attended adverse events (MAAEs), adverse events of special interest (AESIs), and adverse events (AEs) leading to withdrawal throughout study.

3.3 Exploratory Endpoint

cTnI levels at Day 1, Day 4, Day 29, Day 32, and Day 57.

4. Study Design

4.1. Overall Study 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 messenger ribonucleic acid mRNA-1273.712 Coronavirus disease 2019 (COVID19) vaccine in individuals 12 through 30 years of age. The study will be conducted at clinical study sites across the United States.

Participants will receive study intervention by intramuscular (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 pre-injection 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 (i.e., 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 4). Depending on when the study injections or end of study (EOS) is scheduled to be completed, the participant will be asked to 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. 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 (Table 3). This study will be conducted in compliance with the protocol, Good Clinical Practice (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)
- Approximately 2 months of follow-up (28 days after each injection)

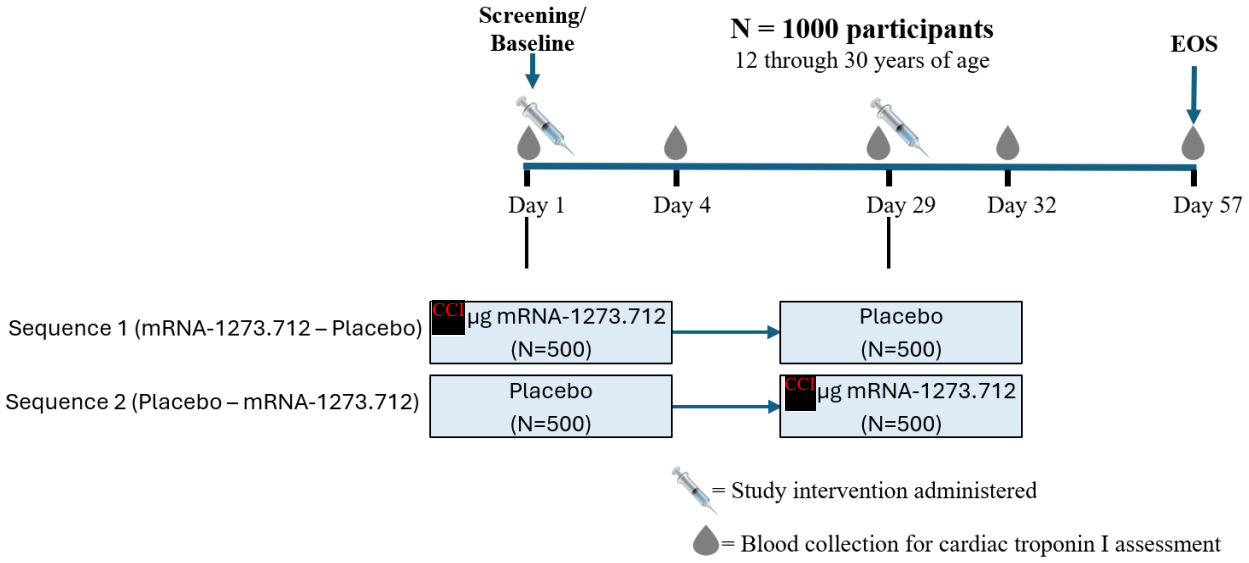
Number of Participants:

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 United States.

Study Interventions:

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

Figure 1: Study Schema



Abbreviation: EOS = end of study

4.2. Sample Size and Randomization

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 CCI µg of mRNA-1273.712 followed by placebo 28 days later (mRNA-1273.712 – placebo [Sequence 1]) or to receive placebo followed by CCI µg of mRNA-1273.712 28 days later (placebo – mRNA-1273.712 [Sequence 2]). Approximately 1000 participants will receive CCI 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 Evaluable Set due to any reasons (e.g., 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%.

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

4.3. Blinding and Unblinding

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. 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.

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.

5. Analysis Populations

The following analysis sets are defined: Randomized Set, Safety Set, and Evaluable Set.

5.1 Randomization Set

The Randomization Set consists of all participants who are randomized in the study, regardless of the participants' treatment status in the study. Participants will be included in the intervention sequence to which they are randomized and analyzed accordingly.

5.2 Safety Set

The Safety Set consists of all randomized participants which receive at least one dose of study intervention. Participants will be included in the intervention sequence corresponding to Injection 1 or Injection 2 received. The safety set will be used for all safety analyses. Analysis will be based on the intervention received rather than the intervention they were randomly assigned.

5.3 Evaluable Set

The Evaluable Set consists of all participants in the Safety Set who have no major protocol deviations or conditions/medications that impact critical or key analysis data. This set will be used for biomarker analyses. Analysis will be based on the intervention group/intervention sequence participants received. Major protocol deviations may include deviations of study procedures/assessments, study treatment admin/dispense (including dosing errors), missing endpoint assessments, concomitant medication, or visiting scheduling. Based on the planned dose of CCI µg, participants with <= 75% or >150% dose level will be excluded from the Evaluable Set.

A few analyses will also use a set called Screen Failed to specifically examine the participants that were screen failures. Participants randomized but not meeting eligibility criteria will also be examined for inclusion/exclusion criteria deviations.

6. Statistical Analysis

6.1. General Considerations

Generally, outputs will be presented by the following intervention sequences as appropriate:

- mRNA-1273.712 – Placebo
- Placebo – mRNA-1273.712
- Total (for cTnI analysis by the intervention sequence and baseline characteristics analysis)

Safety analyses will not use the Total column.

The following intervention groups are defined and will be used for analysis of cTnI and adverse events:

- 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).

Injection at Day 1 will be referred to as Injection 1 and injection at Day 29 will be referred to as Injection 2. 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.

Intervention sequence is defined and will be used for analysis by the following: 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]).

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

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

Categorical variables will be summarized using counts and percentages.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count

tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in the intervention sequence within the analysis set of interest, unless otherwise specified.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug or placebo at Day 1.

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

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

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

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

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

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

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

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

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

Visit window rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing or partial missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing or partial missing AE dates are provided in Appendix D.

- Other incomplete/missing data will not be imputed, unless specified otherwise.

Analyses may be conducted using the following subgroups:

- Age (12 through 17 years and ≥18 through 30 years)
- Sex (female, male) at birth
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific islander, Other, Unknown, Not Reported). Participants with multiple categories of race or that do not fit under any of the other defined categories will be categorized as Other.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

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

6.2. Baseline Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following categories will be summarized by intervention sequence as defined in Section 6.1.

- Randomized Set
- Safety Set
- Evaluable Set

Summary of reasons for participants excluded from Evaluable Set will also be provided.

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

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

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

The number and percentage of participants in each of the following disposition categories will be summarized by intervention sequence based on the Randomized Set:

- Randomized by site
- Received study vaccine

- Prematurely discontinued study vaccine and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

The denominator for all percentages will be the number of participants in the intervention sequences within the Randomized Set.

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

A participant is considered to have completed the study after completion of the last scheduled visit/procedure as shown in the Schedule of Activities (Appendix E).

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of participants will be provided for categorical variables such as age group, sex, race, ethnicity. The summaries will be presented by intervention sequence (mRNA-1273.712 – placebo, placebo – mRNA-1273.712, and Total) based on the Safety Set and Evaluable Set. If the Safety Set differs from the Randomized Set (e.g., participants randomized but did not receive any study injection; participants received study vaccination other than the intervention sequence they were randomized to), the analysis will also be conducted using the Randomized Set.

For screened failure participants, age (years), as well as sex, race, and ethnicity will be presented in a listing.

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

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 27.1). The summaries will be presented by intervention sequence (mRNA-1273.712 – placebo, placebo – mRNA-1273.712, and Total).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events

within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of total intervention sequence group and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD version 202304). The summary of prior and concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 3.

The number and percentage of participants using prior and concomitant medications and non-study vaccination during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by intervention sequences (mRNA-1273.712 – placebo, placebo – mRNA-1273.712, and Total) as follows:

- Any concomitant medications and non-study vaccination (prior medications included) post-Injection 1 up to pre-Injection 2
- Any concomitant medications and non-study vaccination (prior medications included) post-Injection 2
- Any concomitant medications and non-study vaccination (prior medications included) after any injection.

Summary tables of concomitant medications and non-study vaccinations (prior medications included) will be provided by PT in descending order of frequency of the Total group during the 28-day follow-up period after each injection.

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

Concomitant procedures will be presented in a listing.

6.2.5. Study Exposure

Study vaccine administration data will be presented in a listing.

Time on study from randomization, from the first injection, and from the second injection will be summarized based on Safety Set.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a

participant's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by intervention sequence: mRNA-1273.712 – placebo, placebo – mRNA-1273.712, and Total, based on the Randomized Set.

Major protocol deviations will be presented in a listing.

6.3. Biomarker Analysis

Biomarker analyses will be based on the Evaluable Set. In an exploratory fashion, the same analyses done on the Evaluable Set will be repeated for the Safety Set as an additional analysis using the windowing described in Section 9.2. The intervention sequences and intervention groups defined in Section 6.1 will both be used for the biomarker analyses.

cTnI will be measured in units pg/mL. Elevated cTnI is defined as per the threshold described in product insert of the high-sensitivity cardiac troponin I (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. Elevated cTnI values will be defined based on the sex-specific 99th percentile cutoff of the assay that will be used for the study, >53.53 in male and >38.64 in female, with units in pg/mL.

Subgroup analyses will be performed according to the following:

- Age (12 through 17 years, and ≥18 through 30 years)
- Sex (female, male) at birth
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific islander, Other, Unknown, Not Reported). Participants with multiple categories of race or that do not fit under any of the other defined categories will be categorized as Other.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

6.3.1. cTnI Analysis

Analyses will be performed by intervention group (mRNA-1273.712, placebo, and Total) and visit: Day 1 or Day 29 (Pre-Injection 1 or Pre-Injection 2), Day 4 or Day 32 (3 days after Injection 1 or Injection 2), and Day 29 or Day 57 (28 days after Injection 1 or Injection 2); and by intervention sequence (mRNA-1273.712 – placebo, placebo – mRNA-1273.712, and Total) and visit: Day 1 (pre-Injection 1), Day 4 (3 days after Injection 1), Day 29 (pre-Injection 2, 28 days after Injection 1), Day 32 (3 days after Injection 2), and Day 57 (28 days after Injection 2).

Percentages will be based on number of participants within each intervention group or sequence with non-missing cTnI data at each corresponding timepoint.

Statistics will include the number of participants (n), median, min, max, Q1, and Q3. The number of participants with elevated cTnI, or cTnI > elevated cTnI threshold by sex will be also presented, along with the percentages and 95% CI with the Clopper-Pearson method. Difference in percentages of participants with elevated cTnI levels between mRNA-1273.712 and placebo intervention groups, and the corresponding 95% CI will be calculated using the Miettinen and Nurminen method. Change in proportion of elevated cTnI levels from Day 1 (baseline) and/or from Day 29 for subsequent timepoints with the corresponding 95% CI using the adjusted Wald intervals will be measured. This change will be calculated as the difference between the proportion of participants with elevated cTnI at specified subsequent timepoint and the proportion of participants with elevated cTnI at Day 1 or Day 29. These analyses will apply to the primary, secondary, and exploratory endpoints. Additionally, participants with at least one non-missing cTnI data at day of injection, or 3 days after each injection will be summarized and categorized by normal, elevated, and missing values at each corresponding timepoint.

Percentages of elevated cTnI levels and their corresponding 95% CI using the Clopper-Pearson method will be plotted by visit in bar charts for the intervention groups (mRNA-1273.712, and placebo) based on the Evaluable Set. These bar charts will also be produced for the age and sex subgroups. Additionally, changes in proportion of elevated cTnI from Day 1 (baseline) will be presented in line charts for the intervention sequences (mRNA-1273.712 – placebo, and placebo – mRNA-1273.712) based on the Evaluable Set at each visit over time. These line charts will also be generated for the age and sex subgroups. In addition, line charts using Day 29 as baseline instead of Day 1 will be created and repeated for each subgroup.

All cTnI data at each visit will be presented in a listing, with a flag indicating participants with elevated cTnI.

6.3.2 eDiary Findings

A listing of all eDiary findings will be created. There will also be a listing of the eDiary data for participants reporting vigorous physical activity and that have an elevated troponin level. If a participant has elevated troponin at any timepoint, their eDiary data will be listed for all timepoints in this listing.

The eDiary findings will be based on the collection schedule as described in Table 4.

6.4 Safety Analysis

Safety summaries will be presented by study intervention sequence (mRNA-1273.712 – placebo, and placebo – mRNA-1273.712). All safety analyses will be based on the Safety Set.

Safety will be assessed by clinical review of all relevant parameters including SAEs, MAAEs, AEs leading to withdrawal from study vaccine and/or study participation, as well as vital sign measurements.

6.4.1 Adverse Events

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.

The investigator will determine if the criterion for a MAAE is met, which is defined as a medically attended AE that leads to an unscheduled visit to a healthcare practitioner. Refer to Protocol Appendix 2 for the definitions of AESI for this study.

SAEs, MAAEs, AESIs and AEs leading to withdrawal, will be coded by PT and SOC using MedDRA (MedDRA version 27.1) and summarized by intervention sequence, and injection stage (post-Injection 1 up to pre-Injection 2, post-Injection 2, after any injection).

All summary tables (except for the overall summary of AEs) will be presented by SOC and PT for SAEs, MAAEs, AESIs, and AEs leading to withdrawal with counts of participants included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency (any AEs regardless of relationship to study injection) of mRNA-1273.712 within the mRNA-1273.712 - placebo intervention sequence, and then alphabetically within SOC.

When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity (if multiple occurrences of the same event with the same severity are reported by the same participant and any are reported as related, the related event will be used), if participants reported multiple events under the same SOC and/or PT. Thus, if a participant has only an unrelated AE, then the most severe of the unrelated AE will be presented, if a participant has an unrelated and related AE then only the related AE and the most severe of the related AE will be used, and if a participant has only a related AE, then the most severe of the related AE will be presented.

Severity will be determined by using the system of Common Terminology Criteria for Adverse Events (CTCAE), where grade refers to the severity for each AE (grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = fatal/death).

Percentages will be based upon the number of participants in the Safety Set receiving mRNA-1273.712 or placebo within each intervention sequence. Subgroup analyses of the AE data will be performed by age and sex groups as described in Section 6.1.

6.4.1.1. Incidence of Adverse Events

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

- Any unsolicited AEs, defined as SAEs, MAAEs, AESIs, and AEs leading to withdrawal IP and study participation
- Any SAEs
- Any MAAEs
- Any AESIs
- Any unsolicited AEs leading to discontinuation from study vaccine
- Any unsolicited AEs leading to discontinuation from participation in the study

The table will also include number and percentage of participants with unsolicited AEs that are treatment-related in each of the above categories by injection stage.

In addition, separate listings containing individual participant AE data for serious AEs, MAAEs, AESIs, and unsolicited AE leading to discontinuation from study vaccine and unsolicited AEs leading to discontinuation from participation in the study will be provided separately.

6.4.1.2. AEs by System Organ Class and Preferred Term

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

- All SAEs and all SAEs that are treatment-related
- All MAAEs and all MAAEs that are treatment-related
- All AESIs and all AESIs that are treatment-related
- All unsolicited AEs leading to discontinuation from study vaccine and all unsolicited AEs leading to discontinuation from study vaccine that are treatment-related
- All unsolicited AEs leading to discontinuation from participation in the study and all unsolicited AEs leading to discontinuation from participation in the study that are treatment-related

- All unsolicited AEs, defined as SAEs, MAAEs, AESIs, and AEs leading to withdrawal IP and study participation, and all unsolicited AEs that are treatment-related

6.4.1.3. AEs by System Organ Class, Preferred Term and Severity

All AEs will be provided by SOC, PT, and severity by CTCAE grade 1 - 3 (mild, moderate, and severe) using frequency counts and percentages. The same analysis will be repeated for all AEs that are treatment-related. SAEs, MAAEs, AESIs, all unsolicited AEs leading to discontinuation from study vaccine, and all unsolicited AEs leading to discontinuation from participation in the study will be analyzed in a similar fashion with all treatment-related versions analyzed as well. PT will be displayed in descending order of frequency based on the Any column (as opposed to Related column) of mRNA-1273.712.

Any unsolicited AEs reported for participants with elevated troponin may be summarized by severity, along with any treatment-related AEs for these participants.

6.4.1.4. Myocarditis, Pericarditis, Myopericarditis, and Cardiomyopathy

Myocarditis, pericarditis, and myopericarditis will be summarized as per a customized MedDRA query (CMQ) based on PTs in the Center for Disease Control (CDC) case definition of myocarditis, pericarditis, and myopericarditis at the following time intervals: up to 14 days after any injection, up to 14 days after injection 1, and up to 14 days after injection 2. Cardiomyopathy and non-infectious myocarditis, pericarditis, and myopericarditis will also be summarized at the same time intervals. Results will be presented by PT. A listing of suspected cases of myocarditis, pericarditis, and myopericarditis will be provided based on the data adjudicated by the Cardiac Event Adjudication Committee.

6.4.2. Pregnancy Evaluation

Safety laboratory testing will include pregnancy tests.

A pregnancy test will be performed on all female participants of childbearing potential at the Screening Visit and before each vaccine administration (Day 1, Day 29) via point-of-care urine, and as needed at unscheduled visits (urine or serum pregnancy test based on the Investigator's discretion). A follicle-stimulating hormone (FSH) test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status. Pregnancy outcomes (FSH, positive/negative) will be listed.

6.4.3. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. Vital signs will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in

Preventative Vaccine Clinical Trials (DHHS 2007). The values meeting the toxicity grading criteria will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a participant has a vital sign result with Grade 2 or higher abnormality at any post-injection visit, then all results of vital sign measurement for that participant will be presented in the listing.

Observed values and changes from Day 1 (baseline) for all vital sign measurements will be summarized at each visit (including pre- and post-Injection for Day 1 and Day 29) by intervention sequence. Shift from Day 1 (baseline) in the toxicity grades at each visit and shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized by intervention sequence. These analyses will be repeated using Day 29 as baseline instead of Day 1 to measure the change in vital signs after injection 2. Toxicity grades guidelines can be found in Table 5 in Appendix F.

7. Changes from Planned Analyses in Protocol

There are no changes from planned analyses in protocol.

8. References

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

   https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

2. Siemens Healthineers. Siemens Healthcare Diagnostics Inc. 11200498_EN Rev. 09, 2024-04. Atellica IM Analyzer. pp. 1–24, *High-Sensitivity Troponin I (TnIH)*.

9. List of Appendices

9.1. Appendix A Standards for Safety Variable Display in TFLs

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

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

9.2. Appendix B Analysis Visit Windows for Safety, Biomarker and Exploratory Analysis

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

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

Step 2: If the safety and biomarker assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 1 below.

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

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.

If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 1 Visit Windows

Visit	Target Study Day	Visit Window in Study Day	
cTnI (Troponin)			
		Primary Analysis Window [Days, Days]	**Additional Analysis Window [Days, Days]**
Day 1 (Injection 1)	1 (Pre-Injection)	[Pre-dose actual injection 1]	[Pre-dose actual injection 1]
Day 4	4	[Injection 1 date + 2 days, Injection 1 date + 6 days]	[Injection 1 date + 1 day, Injection 2 date – 1 day]
Day 29 (Injection 2)	29 (Pre-Injection)	[Pre-dose actual injection 2]	[Pre-dose actual injection 2]
Day 32	32	[Injection 2 date + 2 days, Injection 2 date + 6 days]	[Injection 2 date + 1 day, Injection 2 date + 14 days]
Day 57	57	[Injection 2 date + 25 days, Injection 2 date + 31 days]	> Injection 2 date + 14 days
Vital Signs			
Day 1, Pre-Injection	1 (Pre-Injection)	≤1 Pre-Injection	N/A
Day 1, Post-Injection	1 (Post-Injection)	[1 Post-Injection, 1]	N/A
Day 4	4	[2, 17]	N/A
Day 29, Pre-Injection	29 (Date of Collection Pre-Injection)	[18, 29 Pre-Injection]	N/A
Day 29, Post-Injection	29 (Date of Collection Post-Injection)	[29 Post-Injection, 31]	N/A
Day 32	32	[32, 45]	N/A
Day 57	57	≥46	N/A

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

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

1. Missing or partially missing medication start date:

   If only Day is missing, use the first day of the month, unless the start month and year of the medication coincide with the start month and year of the first IP injection.

   - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "No"), then use the date of the first IP injection.
   - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "Yes"), then use the earlier of the first day of the month or the date of the first IP injection.
   - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?") is missing and the medication end date is on/after the date of the first IP injection or is missing, then use the date of the first IP injection.

   If Day and Month are both missing, use the first day of the year, unless the start year of the medication coincide with the start year of the first IP injection.

   - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "No"), then use the date of the first IP injection.
   - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "Yes"), then use the earlier of the first day of the year or the date of the first IP injection.
   - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?") is missing and the medication end date is on/after the date of the first IP injection or is missing, then use the date of the first IP injection.

If Day, Month and Year are all missing, the date will not be imputed, but will use the following rules for purposes of determining the status as prior and/or concomitant.

- If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "No"), then the medication will be treated as having begun after first IP injection.
- If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to first study treatment administration?" = "Yes"), or if the mark is missing, then the medication will be treated as a prior medication (and as a concomitant medication unless the stop date indicates the medication was stopped prior to first IP injection).

2. Missing or partial medication stop date:

If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).

If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).

If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 2 below.

Table 2 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Injection**	**≥ First Dose Date and ≤ End Date of Last Study Injection + 27 days**	**> 27 Days After Last Injection [2]**
< First dose date of study vaccination [1]	P	PC	PCA
≥ First dose date and ≤ 27 days after last injection	-	C	CA
> 27 days after last injection	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

9.4. Appendix D Imputation Rules for Missing AE dates

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

1. Missing or partial AE start date:

- If only DAY is missing, use the first day of the month, unless:
  - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.
- If DAY and Month are both missing, use the first day of the year, unless:
  - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection.

- If DAY, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

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

9.5. Appendix E Schedule of Assessments

Table 3: 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 post-injection 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

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**
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 in protocol).

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 4: 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 3). 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.

9.6. Appendix F Vital Signs Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Appendix E Schedule of Assessments

Table 5: Severity Grading of Vital Sign Abnormalities

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTx, Inc.**
Protocol Number:	**mRNA-1273-P404**

Document Description:	Statistical Analysis Plan
SAP 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
SAP Version Number:	1.0
Effective Date:	18 February 2025

Author(s):

For PPD: PPD

Approved by:

PPD

18-Feb-2025

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

PPD

18-Feb-2025

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

PPD

18-Feb-2025

Date (DD-MMM-YYYY)

ModernaTX, Inc.

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with Docusign: Moderna mRNA-1273-P404 SAP v1.0_Signature Form.docx
Source Envelope:
Document Pages: 1
Signatures: 3
Certificate Pages: 3
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Monrovia, Reykjavik

Envelope Originator:
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929 N Front St
Wilmington, NC 28401
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IP Address: PPD

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Status: Original
18 February 2025 | 18:44

Holder: PPD

Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 18 February 2025 | 19:12 Viewed: 18 February 2025 | 19:16 Signed: 18 February 2025 | 19:17
Electronic Record and Signature Disclosure: Accepted: 18 February 2025 | 19:16 ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 18 February 2025 | 19:12 Viewed: 18 February 2025 | 19:16 Signed: 18 February 2025 | 19:17
Electronic Record and Signature Disclosure: Accepted: 18 February 2025 | 19:16 ID: PPD		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 18 February 2025 | 19:12 Viewed: 18 February 2025 | 19:13 Signed: 18 February 2025 | 19:18
Electronic Record and Signature Disclosure: Accepted: 18 February 2025 | 19:13 ID: PPD		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	18 February 2025 | 19:12
Certified Delivered	Security Checked	18 February 2025 | 19:13
Signing Complete	Security Checked	18 February 2025 | 19:18
Completed	Security Checked	18 February 2025 | 19:18

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures