Amsterdam, 13 November 2025
EMADOC-1700519818-2360320
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report for Paediatric Studies submitted in accordance with Article 46 of Regulation (EC) No 1901/2006

Spikevax

COVID-19 mRNA vaccine

Procedure no.: EMA/PAM/0000291853

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start date	15 September 2025	15 September 2025
☐	CHMP Rapporteur AR	20 October 2025	17 October 2025
☐	CHMP comments	3 November 2025	3 November 2025
☐	Updated CHMP Rapporteur AR	6 November 2025	N/A
☒	CHMP outcome	13 November 2025	13 November 2025

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1. Introduction

On 13 August 2025, the MAH submitted a completed paediatric study for Spikevax, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study mRNA-1273-P404 – A Phase 4, Randomised, Observer-blind, Placebo-controlled, Crossover Study to Assess Cardiac Troponin Levels after mRNA-1273.712 Vaccine in Participants 12 through 30 years of age is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study was conducted between October 2024 and January 2025 in the United States (US) using the US Food and Drug Administration approved 2024 vaccine formulation: mRNA-1273.712 (Omicron KP.2 monovalent). Participants aged 12 through 17 years (433 out of 997 participants in the Safety Set) received the same Omicron KP.2 monovalent formulation and dose as for adult participants. Study injections, mRNA-1273.712 and saline placebo, were administered intramuscularly.

Of note, Spikevax variant-adapted vaccine mRNA-1273.712 (Omicron KP.2 monovalent) has been submitted for approval in the EU on 28 March 2025 but submission has been withdrawn on 10 June 2025 (date of consolidating sequence). Therefore, Spikevax mRNA-1273.712 has not been approved in the EU.

Spikevax mRNA-1273.712 was approved by the US FDA in the United States (US) during study conduct.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- mRNA-1273-P404 – A Phase 4, Randomised, Observer-blind, Placebo-controlled, Crossover Study to Assess Cardiac Troponin Levels after mRNA-1273.712 Vaccine in Participants 12 through 30 years of Age.

Myocarditis related to SARS-CoV-2 infection has been reported since the beginning of the pandemic. The relative risk of myocarditis is significantly higher in individuals with SARS-CoV-2 infection (15.0 [95% CI: 11.09, 19.81]) compared with those who received mRNA COVID-19 vaccines (2.0 [95% CI: 1.44, 2.65]). This indicates that the risk of myocarditis is over 7 times greater following infection than after vaccination (Voleti et al 2022). The prevalence of cardiac complications in adults after being diagnosed with COVID-19 includes heart failure (23% to 33.3%), myocardial injury/myocarditis (8% to 27.8%), arrhythmia (16.7%), and thromboembolism (31% to 40%).

Post-marketing data with authorised or approved mRNA COVID-19 vaccines, including Spikevax, have demonstrated increased risks of myocarditis and pericarditis as a very rare event (frequency <1 event

per 10,000 doses administered), with onset of symptoms typically in the first week following vaccination, especially after a second dose of the vaccine. For Spikevax, the observed risk is highest in males 12 years through 24 years of age, with an estimated unadjusted incidence of myocarditis and/or pericarditis during the period of 1 through 7 days of approximately 25 cases per million doses in this age group. These events are generally mild, and often self-limiting, with resolution of symptoms within a few days with conservative management; however, these events are not well understood, including underlying pathogenesis and risk factors for myocarditis and pericarditis.

Cardiac Troponin I (cTnI) is a biomarker used to measure myocardial injury and is routinely employed in the diagnosis of myocardial infarction. Troponin I elevations provide evidence of cell degradation and allow identification of damaged cardiac tissue such as necrosis associated with myocarditis. Elevated cTnI is not specific to determine the cause of the myocardial injury, and cTnI levels may also be elevated in association with other cardiac and noncardiac processes and conditions, including stress, exercise, rhabdomyolysis, and autoimmunity (McCarthy et al 2019, Wu 2017, Goldmann et al 2001). The relationship of elevated cTnI to non-pathogenic processes, such as vigorous exercise, is known (Aakre and Omland 2019, Conesa-Milian et al 2023). Furthermore, cTnI levels have not been studied extensively in adolescents or young adults.

The submitted Phase 4 randomised, placebo-controlled, crossover study was conducted in the United States between October 2024 and January 2025 to assess cTnI levels after injection with mRNA-1273.712 and placebo in adolescent and young adult participants 12 through 30 years of age. The crossover study design allowed comparison of cTnI elevation before and after mRNA-1273.712 vaccination versus placebo in the age group that is at the highest risk for COVID-19 vaccine-associated myocarditis.

2.3.2. Clinical study

Study mRNA-1273-P404

Description

This was a Phase 4, randomised, observer-blind, placebo-controlled, crossover clinical study to assess cTnI levels after injection with the KP.2 variant-containing mRNA-1273.712 COVID-19 vaccine in adolescent and young adult participants 12 through 30 years of age.

Methods

Study participants

Approximately 1000 participants were planned to be enrolled and randomised in a 1:1 ratio (approximately 500 participants in each injection sequence) to receive 2 study injections (mRNA-1273.712 and placebo) in a crossover design. At least 45% of participants were planned to be enrolled in each of the age groups (12 through 17 years and 18 through 30 years).

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 of the protocol) which includes compliance with the requirements and restrictions listed in the ICF and in the 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 fulfils 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 (e.g., 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 protocol 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.

Exclusion Criteria

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

5. 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.

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

7. Has a documented history of myocarditis or pericarditis.

8. 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.

9. 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/m2 (>20 years) or severe obesity defined as BMI for sex and age ≥120% of the 95th percentile [BMI ≥35 kg/m2] (for 12 to 20 years) (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm)
- Other conditions – see Protocol table 8:
- Protocol 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)

10. 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.
11. 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.
12. 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.
13. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections disease.
14. History of Guillain-Barré syndrome.
15. Coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.
16. History of malignancy within previous 5 years (excluding nonmelanoma skin cancer).
17. 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.

18. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
19. 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.
20. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

Assessor's comment:

Overall, the Inclusion and Exclusion criteria are reasonable in order to investigate the effect of vaccination with Spikevax on the elevation of cTnI in subjects with a reduced risk of elevated cTnI.

Treatments

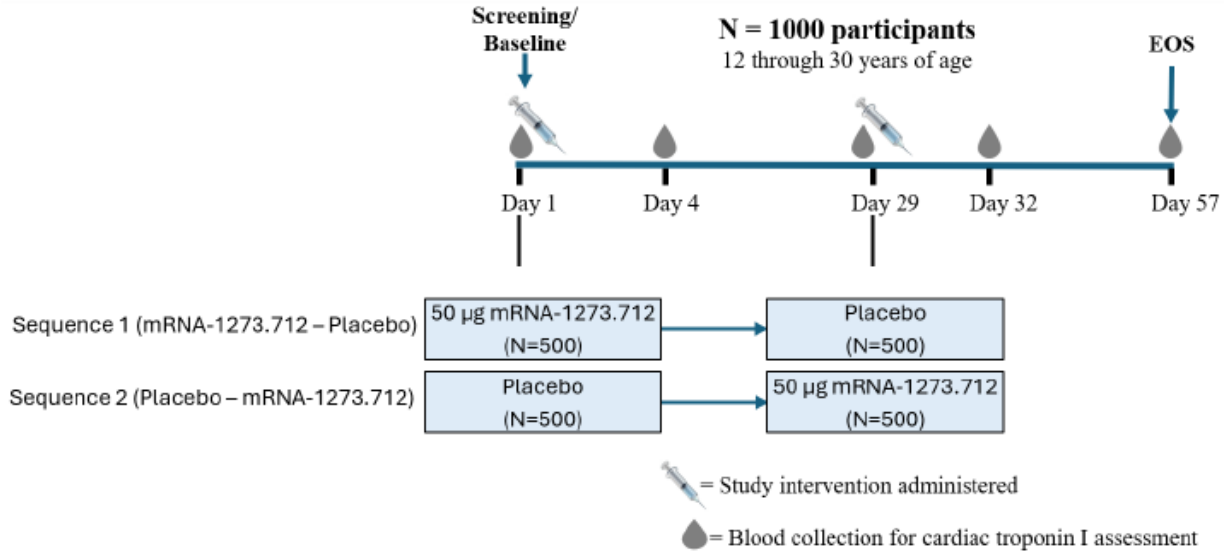
Participants received either 50 µg of mRNA-1273.712 followed by placebo 28 days later (Sequence 1) or placebo followed by 50 µg of mRNA-1273.712 28 days later (Sequence 2). Each participant received IM injection on Day 1 and Day 29 according to their assigned sequence. At each visit when study injection was administered, participants were monitored for a minimum of 15 minutes after administration. The interval between the 2 study injections was not expected to introduce any carryover effects given that troponin elevations are expected to persist for a few days to a couple of weeks, depending on the underlying cause.

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

Blood samples were collected from all participants pre-injection on the day of each injection, as well as 3 and 28 days after each injection for assessment of cTnI. To aid in interpretation of cTnI assessment, participants were to record vigorous physical activities in an eDiary. Depending on when the study injections or EOS were scheduled to be completed, the participant was to complete the eDiary for 4 consecutive days post-Injection 1 (Day 1), 4 consecutive days pre- and post-Injection 2 (Day 29), 4 consecutive days prior to the EOS visit (Day 57), and on the day of the EOS visit. Participants were encouraged, but not required, to avoid vigorous physical activities, when possible, for 4 days before and after each injection.

The study was comprised of 5 scheduled in-clinic visits. Participants were in the study for approximately 2 months, including 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).

The study schema is illustrated in Figure 1.



Abbreviation: EOS = end of study.

Figure 1 Study Design

Assessor's comment:

The design of study P404 allows to compare levels of cTnI prior to and after vaccination versus placebo.

Objectives and endpoints

The objectives and endpoints of this study are presented in Table 1.

Table 1 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.

Study Interventions

Study Interventions Administered

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 was to receive 50 µg of mRNA-1273.712 and placebo in a crossover design with the following sequences:

- Sequence 1 (mRNA-1273.712 – placebo): 50 µg of mRNA-1273.712 followed by placebo 28 days later
- Sequence 2 (placebo – mRNA-1273.712): placebo followed by 50 µg of mRNA-1273.712 28 days later

The study injections are outlined in Table 2.

Table 2 Study Injections Administered

Injection Name	mRNA-1273.712	Placebo
Dose	50 µg	NA
Lot number	Y000011927	6034684
Dosage form	Dispersion for injection	Sodium chloride for injection
Route of administration	IM injection	IM injection

Abbreviations: IM = intramuscular; NA = not applicable.

Prior and Concomitant Therapy

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 was collected. All previous COVID-19 vaccinations received prior to informed consent/assent were recorded.

During the study, the study staff questioned the participant and/or their legally authorised representative and recorded any reportable medication including non-study vaccinations. The use of concomitant medications and/or vaccines may have resulted in the participant's exclusion from analyses based on the Evaluable Set.

Safety Assessments

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

- AEs leading to withdrawal of study injection and/or study participation 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 in persons of childbearing potential were collected after the start of study injection and until the end of their participation in the study. All pregnancies were to be followed to determine the outcome; however, pregnancy-related data received after the EOS may not have been collected in the clinical database.
- Concomitant medications and non-study vaccinations.

No scheduled laboratory assessments for safety were planned. Additional details regarding the collection of safety assessments are provided in Section 8.2 and Section 8.3 of the protocol (Appendix 16.1.1, not shown here).

An independent CEAC reviewed all suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they met CDC case definition (Gargano et al 2021) as "probable" or "confirmed" events.

Assessor's comment:

Applying the CDC case definition for probable or confirmed myocarditis, pericarditis, and myopericarditis events is acceptable for the purpose of the study.

Biomarker Assessments

Blood samples for assessment of cTnI levels were collected from all participants at the following timepoints:

- 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 were based on the sex-specific 99th percentile cut-off of the Atellica IM High-sensitivity Troponin I assay used in this study, defined as >53.53 pg/mL for males and >38.64 pg/mL for females. The LLOQ was 3 pg/mL for the cTnI assay.

Expected values for the assay were established using the Atellica IM Analyzer and verified on the Atellica CI Analyzer. The 99th percentile values were determined using the non-parametric statistical method described in CLSI Document EP28 A3c. Using the 99th percentile ensures high sensitivity (i.e., detecting most true positives) while maintaining reasonable specificity (i.e., limiting false positives from non-cardiac causes).

Assessor's comment:

Use of the Atellica IM High-sensitivity Troponin I assay is appropriate for the purpose of this study.

eDiary Assessments

To aid interpretation of cTnI assessment, participants were to record vigorous physical activities in an eDiary. Depending on when the study injections or EOS were scheduled to be completed, the participant was 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 the EOS visit (Day 57), and on the day of the EOS visit. Participants were encouraged, but not required, to avoid vigorous physical activities, when possible, for 4 days before and after each injection.

Per protocol, vigorous physical activities were defined as activities that required hard physical effort and made the participant breathe much harder than normal as these types of activities can elevate cTnI levels (Aakre and Omland 2019). The eDiary did not include all possible vigorous physical activities, instead contained the following selection of activities typical for this age group that had the potential to result in elevated cTnI:

- Jog/run
- Swim/water exercise
- Play organized sport
- Ride bicycle
- Lift weights/use stationary weight machine
- Heavy manual labour

Assessor's comment:

As physical activities are known to enhance cTnI levels the implementation of the eDiary is appropriate.

Sample size

Approximately 1000 participants will be randomised in a 1:1 ratio to one of 2 intervention sequences (approximately 500 participants in each intervention sequence) in this study, to receive 50 µg of mRNA- 1273.712 followed by placebo 28 days later (mRNA-1273.712 – placebo [Sequence 1]) or to

receive placebo followed by 50 µg of mRNA-1273.712 28 days later (placebo – mRNA-1273.712 [Sequence 2]). Approximately 1000 participants will receive 50 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%.

Assessor's comment:

Study P404 enrolled 1000 subjects in total. With the observed rate of myocarditis/pericarditis of <1 in 10 000 doses administered it cannot be expected that events of myocarditis/pericarditis are observed in this study. A study that is meant to detect cases of myocarditis/pericarditis is not feasible due to the large number of subjects that would be needed.

The information that can be gathered from this study and its sample size is whether there is an elevation of cTnI after vaccination with mRNA.1273.712 indicative for myocardial injury.

Randomisation and blinding (masking)

Assignment to Study Intervention

Random assignment of participants made use of a centralized IRT, in accordance with pre-generated randomisation schedules.

This study is an observer-blind study. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded as per SAP, V1.0 (18Feb2025) to the study intervention administered until study end. Unblinded pharmacy personnel (of limited number) were to be assigned to study intervention accountability procedures and did prepare and administer mRNA-1273.712 or placebo to all participants. Unblinded study site monitors, not involved with other aspects of monitoring, were 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 should remain blinded until the EOS.

Statistical Methods

Analysis Populations

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

Randomisation Set

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

Safety Set

The Safety Set consists of all randomised 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.

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 50 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 randomised but not meeting eligibility criteria will also be examined for inclusion/exclusion criteria deviations.

General Considerations

Biomarker analyses were performed by injection group and injection sequence. As described previously, the following injection groups were defined:

- mRNA-1273.712 group: participants who received mRNA-1273.712 for Injection 1 in Sequence 1 and participants who received mRNA-1273.712 for Injection 2 in Sequence 2.
- Placebo group: participants who received placebo for Injection 1 in Sequence 2 and participants who received placebo for Injection 2 in Sequence 1.

Safety analyses were performed by injection sequence only.

Biomarker (cTnI) Analysis

cTnI was assessed longitudinally on a participant level. All statistical analyses for cTnI levels were descriptive.

A participant may have been included in both the 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) was summarised for the mRNA-1273.712 group and placebo group in the Evaluable Set.

The secondary endpoints of the proportion of participants with elevated cTnI at pre-Injection 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) were summarised for the mRNA-1273.712 group and placebo group in the Evaluable Set.

In addition, the proportion of participants with elevated cTnI at each timepoint (Day 1, Day 4, Day 29, Day 32, and Day 57) was summarised for the mRNA-1273.712 group and placebo group and for each injection sequence. If an elevated cTnI level was detected during the analysis, the activity data for that participant was reviewed for correlation of vigorous physical activities with elevated cTnI levels.

The number and proportion of participants with elevated cTnI levels (>threshold) at specified timepoints were summarised, along with 95% CIs using the Clopper-Pearson method. The 95% CI for the difference in proportions between the mRNA-1273.712 and placebo groups was calculated using the Miettinen Nurminen method. The change in proportion of elevated cTnI levels from pre-Injection

Day 1 and/or from pre-Injection Day 29 to subsequent timepoints within injection groups, along with the corresponding 95% CI, were calculated using the adjusted Wald intervals for paired data.

Safety Analysis

All safety analyses were based on the Safety Set.

Safety assessments were based on the unsolicited AEs collected in this study including SAEs, MAAEs, AESIs, and AEs leading to withdrawal of study injection and/or study participation, as well as vital sign measurements and physical examination findings. Reactogenicity has been well characterized in other studies; therefore, solicited adverse reactions were not collected during this study.

The number and percentage of participants with SAEs, MAAEs, AESIs, and AEs leading to withdrawal were summarised. Unsolicited AEs were coded by SOC and PT according to MedDRA version 27.1.

The number of events of SAEs, MAAEs, AESIs, and AEs leading to withdrawal were reported in summary tables using descriptive statistics.

The safety summaries were presented by injection sequence and for participants who received at least 1 dose of study injection.

Pregnancy outcomes were also summarised.

Assessor's comment:

Solicited AEs have not been collected in this study since the reactogenicity after vaccination with mRNA-1273 variants has been well characterized which is acceptable for the purpose of the study.

Subgroup Analysis

Subgroup analyses for cTnI were performed according to the following:

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

Subgroup analysis for safety was performed by age group and sex.

Adverse Events of Interest (Investigator-assessed AESIs and Programmed SMQs and CMQs)

- Identification of AEs of interest used the overlapping strategies described below. Events that have been identified using these strategies are described in the following sections, grouped by medical category. Case descriptions are included for relevant events.
- Investigator-assessed AESIs: Investigators were to report unsolicited AEs as AESIs based on definitions provided in Section 10.2 of the protocol (not shown here). Investigators were to report all suspected cases of myocarditis, pericarditis, or myopericarditis. Those cases were submitted to the independent CEAC for adjudication following the CDC case definition for acute myocarditis and pericarditis (Gargano et al 2021) as "probable" or "confirmed" myocarditis, pericarditis, or myopericarditis or as "not a charter-define case."

- Programmed SMQs for Cardiomyopathy and Non-infectious Myocarditis, Pericarditis, or Myopericarditis: All reported unsolicited AEs (regardless of Investigator assessment as AESI) were queried using MedDRA SMQs (narrow + broad scope).
- Supplemental CMQ for Myocarditis and Pericarditis: Case detection for PTs reported within 14 days of study injection and potentially indicative of myocarditis and pericarditis was performed using a CMQ (based on the CDC working case definition for myocarditis and pericarditis; Gargano et al 2021). This approach focused on the identification of signs or symptoms that may be associated with myocarditis or pericarditis. All cases within 14 days of study injection were then medically reviewed by the Sponsor.

Assessor's comment:

AEs of special interest were searched by investigator reported AESIs and by programmed SMQs and supplemental CMQs which is acknowledged.

Results

Participant flow

Disposition of Participants

Among the 1000 participants who were randomised, 997/1000 (99.7%) participants received at least 1 dose of study injection (500/500 [100%] in Sequence 1 and 497/500 [99.4%] in Sequence 2) (Table 3 and Figure 2).

A total of 83/1000 (8.3%) participants discontinued study injection (39/500 [7.8%] in Sequence 1 and 44/500 [8.8%] in Sequence 2). The most frequent reasons for discontinuation of study injection were lost to follow-up (22/500 [4.4%] in Sequence 1 and 26/500 [5.2%] in Sequence 2), followed by withdrawal of consent (12/500 [2.4%] in Sequence 1 and 15/500 [3.0%] in Sequence 2).

A total of 136/1000 (13.6%) participants were discontinued from the study (62/500 [12.4%] in Sequence 1 and 74/500 [14.8%] in Sequence 2). The most frequent reasons for study discontinuation were lost to follow-up (46/500 [9.2%] in Sequence 1 and 48/500 [9.6%] in Sequence 2), followed by withdrawal of consent (12/500 [2.4%] in Sequence 1 and 21/500 [4.2%] in Sequence 2).

Table 3 Participant Disposition (Randomised Set)

	Sequence 1	Sequence 2	
	mRNA-1273.712 – Placebo (N=500) n (%)	Placebo – mRNA-1273.712 (N=500) n (%)	Total (N=1000) n (%)
Number of participants			
Received study injection	500 (100)[a]	497 (99.4)[b]	997 (99.7)
Discontinued study injection	39 (7.8)	44 (8.8)	83 (8.3)
Reason for discontinuation			
AE[c]	2 (0.4)	1 (0.2)	3 (0.3)
Death	0	0	0
Lost to follow-up	22 (4.4)	26 (5.2)	48 (4.8)
Physician decision	0	1 (0.2)	1 (0.1)
Pregnancy	3 (0.6)	0	3 (0.3)
Protocol deviation	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal of consent	12 (2.4)	15 (3.0)	27 (2.7)
Other	0	1 (0.2)	1 (0.1)

	Sequence 1	Sequence 2	
	mRNA-1273.712 – Placebo (N=500) n (%)	Placebo – mRNA-1273.712 (N=500) n (%)	Total (N=1000) n (%)
Completed study[d]	438 (87.6)	424 (84.8)	862 (86.2)
Discontinued from study	62 (12.4)	74 (14.8)	136 (13.6)
Reason for discontinuation			
AE	0	1 (0.2)	1 (0.1)
Death	0	0	0
Lost to follow-up	46 (9.2)	48 (9.6)	94 (9.4)
Physician decision	3 (0.6)	3 (0.6)	6 (0.6)
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal of consent	12 (2.4)	21 (4.2)	33 (3.3)
Other	1 (0.2)	1 (0.2)	2 (0.2)

Abbreviations: AE = adverse event; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary.

[a] One participant erroneously received placebo followed by mRNA-1273.712 for the first and second injections, respectively, due to dosing error.

[b] One participant erroneously received mRNA-1273.712 for the first injection due to dosing error.

[c] One participant initially had their second dose delayed due to an AE of abnormal ECG (action taken in the AE eCRF was recorded as dose delayed). Following repeat testing that was normal, the participant was scheduled to return for the second injection but did not return for the visit despite rescheduling. The reason for discontinuation of study injection was reported as due to the AE in the disposition eCRF, and the reason for discontinuation from the study was reported as physician decision, due to the participant's non-compliance with the visit schedule and eDiary completion.

[d] Participants were considered to have completed the study if they completed the last scheduled procedure on Day 57. Two participants were screen failures who were randomized in error. These 2 participants were not counted as completed the study nor discontinued from the study.

Source: Table 14.1.1.1

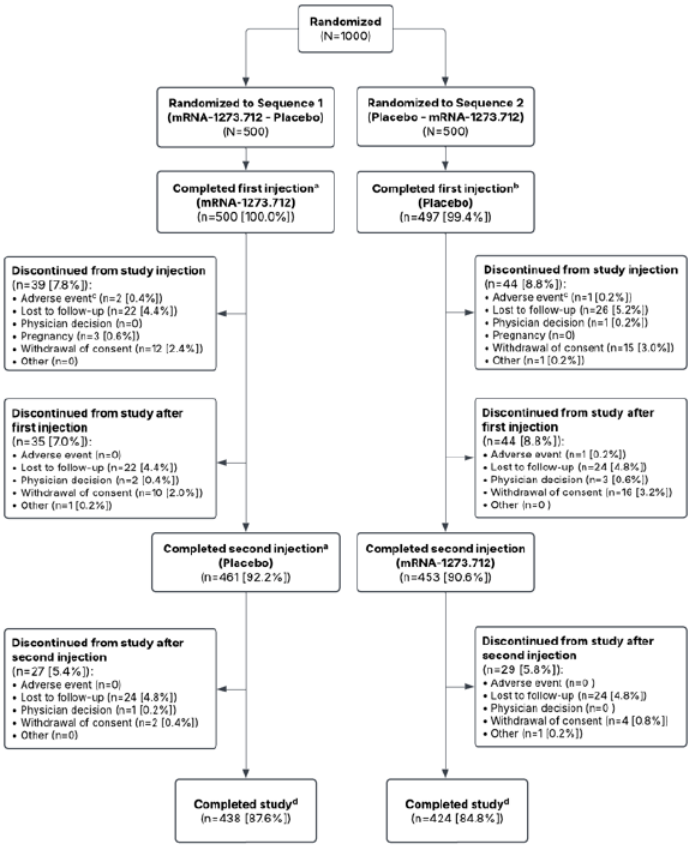


Figure 2 Participant Disposition (Randomised Set)

[a] Includes 1 participant who erroneously received placebo followed by mRNA-1273.712 for the first and second injections, respectively, due to dosing error.

[b] Includes 1 participant who erroneously received mRNA-1273.712 for the first injection due to dosing error.

[c] One participant initially had their second dose delayed due to an AE of abnormal ECG (action taken in the AE eCRF was recorded as dose delayed). Following repeat testing that was normal, the participant was scheduled to return for the second injection but did not return for the visit despite rescheduling. The reason for discontinuation of study injection was reported as due to the AE in the disposition eCRF, and the reason for discontinuation from the study was reported as physician decision, due to the participant's non-compliance with the visit schedule and eDiary completion.

[d] Participants were considered to have completed the study if they completed the last scheduled procedure on Day 57. Two participants were screen failures who were randomized in error. These 2 participants were not counted as completed the study nor discontinued from the study.

Source: Table 14.1.1.1 and Listing 16.2.1.1

Protocol Deviations

At least 1 major protocol deviation was reported in 88/500 (17.6%) and 97/500 (19.4%) participants in Sequence 1 and Sequence 2, respectively; most were related to study procedures or assessments, such as visit not performed, visit performed out of window or blood sample not collected per protocol (80/500 [16.0%] and 87/500 [17.4%] participants, respectively). Review of the protocol deviations did not identify a meaningful impact to overall data integrity, data analysis, and participant safety.

Recruitment

Analysis Sets

A total of 1000 participants were randomised in this study (500 participants to each injection sequence). Three participants in Sequence 2 did not receive any study injection and were excluded from the Safety Set.

The Evaluable Set included 491/500 (98.2%) and 490/500 (98.0%) participants in Sequence 1 and Sequence 2, respectively. Participants were excluded from the Evaluable Set for having major protocol deviations or conditions/medications that impacted key analysis data. The most common reason for exclusion from the Evaluable Set was participants who had major protocol deviations that impacted the Evaluable Set analysis (10/1000 [1.0%]), followed by use of a prohibited medication/vaccination (4/1000 [0.4%]).

Baseline data

Demographics and Baseline Characteristics

Overall, 528/981 (53.8%) participants were female. Most participants were White (639/981 [65.1%]), followed by Black or African American (236/981 [24.1%]), with ethnicity reported as non-Hispanic/non-Latino in 823/981 (83.9%) participants. The median age was 18.0 years (range: 12 to 30 years), with 536/981 (54.6%) participants who were between 18 to 30 years of age. The median weight was 68.4 kg (range: 28.0 to 142.5 kg), and the median body mass index was 24.0 kg/m2 (range: 12.6 to 39.9 kg/m2).

In the Evaluable Set, demographics were similar between the injection sequences. The mean ages were 19.6 and 20.0 years in sequence 1 and sequence 2, respectively. There were 47.5% and 43.3% of the participants in the age group ≥12 to ≤17 years, and 53.2% and 54.5% were female in sequence 1 and sequence 2, respectively.

Assessor's comment:

Demographics for subjects included in this study were balanced and appropriate.

Medical History

Overall, medical history was reported in 622/997 (62.4%) participants. The most frequently reported (≥5% overall) medical history conditions were anxiety (183/997 [18.4%]), attention deficit hyperactivity disorder (156/997 [15.6%]), depression (155/997 [15.5%]), seasonal allergy (139/997 [13.9%]), asthma (98/997 [9.8%]), acne (66/997 [6.6%]), and drug hypersensitivity (56/997 [5.6%]). The medical history of participants in this study was representative of typical conditions in adolescents and young adults.

Prior and Concomitant Therapy

Approximately half of the participants (501/997 [50.3%]) reported at least 1 concomitant medication during the study. The most frequently reported (≥5% overall) concomitant medications were salbutamol (63/997 [6.3%]) and amphetamine aspartate/amphetamine sulfate/dexamphetamine saccharate/dexamphetamine sulfate (50/997 [5.0%]).

Number analysed

Efficacy results

Not applicable

Safety results

Extent of Exposure

Safety data are presented for a total of 997 participants who received at least 1 dose of study injection (Safety Set), of which 954 participants received at least 1 dose of mRNA-1273.712. A total of 914 (91.7%) participants also received the second dose of study injection (460/500 [92.0%] participants in Sequence 1 and 454/497 [91.3%] participants in Sequence 2). The median duration of study participation from the first study injection was 57.0 days in both Sequence 1 (range: 1 to 104 days) and Sequence 2 (range: 1 to 98 days).

Solicited Adverse Reactions

Solicited adverse reactions were not collected during this study.

Unsolicited AEs

The unsolicited AEs collected in this study consisted of SAEs, MAAEs, AESIs, and AEs leading to discontinuation of study injection and/or from study participation. No new safety concerns were identified for mRNA-1273.712 following review of the unsolicited AEs.

Sequence 1 (mRNA-1273.712 – Placebo)

In Sequence 1 with 500 participants, unsolicited AEs occurred in 6 (1.2%) after the mRNA-1273.712 injection (2 mild unsolicited AEs and 4 moderate unsolicited AEs) and in 5 (1.1%) after the placebo injection (3 mild unsolicited AEs and 2 moderate unsolicited AEs). All unsolicited AEs reported were MAAEs.

In the adolescent age group, 5/235 (2.1%) participants reported unsolicited AEs after the mRNA-1273.712 injection and no unsolicited AEs were reported after the placebo injection. There were no SAEs (including fatal events) reported in Sequence 1. One participant had an AESI of seizure which led to discontinuation of study injection. All of the events reported after the mRNA-1273.712 injection were reported in 1 participant each.

Additionally, there was 1 participant in the adolescent age group with a non-serious event of ECG abnormal associated with transient chest pain and elevated cTnI after the mRNA-1273.712 injection. As this was the only unsolicited AE associated with an elevated cTnI reported during the study, a brief narrative of the case is provided below. The cTnI levels for this participant (and all participants with elevated cTnI levels) are summarised in Table 5.

- **ECG abnormal:** A 14-year-old male with elevated cTnI of 183 pg/mL on Day 1, prior to receipt of study injection, had elevated cTnI of 1588 pg/mL on Day 4, the routine study blood draw, 3 days after receipt of mRNA-1273.712. The participant's mother confirmed that the participant, who was a cross-country runner, had been running in the days prior to the Day 4 blood draw and had been asymptomatic at that time. At the Day 29 visit, the mother reported that the participant had some transient chest pain while running in the days prior to the visit. The ECG obtained was interpreted as abnormal by the Investigator. The participant was asymptomatic at that time but was sent to the local emergency department for further evaluation and the second study injection was not administered. A cardiac workup was performed including ECG, troponins×2, chest X-ray, cardiac ultrasound, complete blood count, and metabolic panel. The troponin was undetectable, and all other tests were within normal limits. The site recorded a mild, non-serious AE of ECG abnormal (reported verbatim: abnormal EKG). This case, including the medical records from the emergency department visit, was sent to the CEAC who adjudicated the event as "not a charter defined event".

In Sequence 1, in the adult age group, 1/265 (0.4%) participant reported unsolicited AEs after the mRNA 1273.712 injection and 5/235 (2.1%) participants reported unsolicited AEs after the placebo injection. One participant had an AESI of atrial fibrillation after the placebo injection. No SAEs (including fatal events) and no AEs leading to discontinuation were reported in Sequence 1. The only event reported in >1 participant was respiratory syncytial virus infection, reported in 2/235 (0.9%) participants after the placebo injection; all other unsolicited AEs after the mRNA 1273.712 and placebo injections were reported in 1 participant each.

None of the unsolicited AEs reported in Sequence 1 were assessed as related to study injection by the Investigator.

Sequence 2 (Placebo – mRNA-1273.712)

In Sequence 2 with 497 participants, 10 unsolicited AEs occurred in 9 subjects (1.8%) after the placebo injection (no mild unsolicited AEs and 10 moderate unsolicited AEs) and 12 AEs occurred in 10 subjects (2.2%) after the mRNA-1273.712 injection (4 mild unsolicited AEs and 8 moderate unsolicited AEs). All unsolicited AEs reported were MAAEs.

In Sequence 2, in the adolescent age group, no unsolicited AEs were reported after the placebo injection and 3/198 (1.5%) participants reported unsolicited AEs after the mRNA-1273.712 injection. One participant had an SAE of suicidal ideation. No AESIs or AEs leading to discontinuation were reported in Sequence 2. All of the events reported after the mRNA-1273.712 injection were reported in 1 participant each.

In Sequence 2, in the adult age group, 9/283 (3.2%) participants reported unsolicited AEs after the placebo injection and 7/256 (2.7%) participants reported unsolicited AEs after the mRNA-1273.712 injection. One participant had 2 events (rash and urinary tract infection) after the placebo injection that led to discontinuation of study injection, and the rash also led to study discontinuation. No SAEs (including fatal events) were reported. The only event reported in >1 participant was bronchitis, reported in 2/283 (0.7%) participants after the placebo injection; all other unsolicited AEs after the mRNA-1273.712 and placebo injections were reported in 1 participant each.

None of the unsolicited AEs reported in Sequence 2 were assessed as related to study injection by the Investigator.

Unsolicited AEs by Subgroups

There were no notable differences observed for unsolicited AEs summarised by sex (Table 4).

Table 4 Overall Summary of Unsolicited AEs After Any Injection by Subgroups (Safety Set)

	Sequence 1		Sequence 2	
	mRNA-1273.712 – Placebo		Placebo – mRNA-1273.712	
	mRNA-1273.712	Placebo	Placebo	mRNA-1273.712
12 to 17 years	**(N=235)**	**(N=225)**	**(N=214)**	**(N=198)**
All	5 (2.1)	0	0	3 (1.5)
Serious	0	0	0	1 (0.5)
Medically attended	5 (2.1)	0	0	3 (1.5)
Leading to discontinuation of study injection	1 (0.4)	0	0	0
Leading to study discontinuation	0	0	0	0
AE of special interest (AESI)	1 (0.4)	0	0	0
18 to 30 years	**(N=265)**	**(N=235)**	**(N=283)**	**(N=256)**
All	1 (0.4)	5 (2.1)	9 (3.2)	7 (2.7)
Serious	0	0	0	0
Medically attended	1 (0.4)	5 (2.1)	9 (3.2)	7 (2.7)
Leading to discontinuation of study injection	0	0	1 (0.4)	0
Leading to study discontinuation	0	0	1 (0.4)	0
AE of special interest (AESI)	0	1 (0.4)	0	0
Female	**(N=265)**	**(N=244)**	**(N=272)**	**(N=246)**
All	4 (1.5)	4 (1.6)	4 (1.5)	5 (2.0)
Serious	0	0	0	0
Medically attended	4 (1.5)	4 (1.6)	4 (1.5)	5 (2.0)
Leading to discontinuation of study injection	0	0	1 (0.4)	0
Leading to study discontinuation	0	0	1 (0.4)	0
AE of special interest (AESI)	0	0	0	0
Male	**(N=235)**	**(N=216)**	**(N=225)**	**(N=208)**
All	2 (0.9)	1 (0.5)	5 (2.2)	5 (2.4)
Serious	0	0	0	1 (0.5)
Medically attended	2 (0.9)	1 (0.5)	5 (2.2)	5 (2.4)
Leading to discontinuation of study injection	1 (0.4)	0	0	0

	Sequence 1		Sequence 2	
	mRNA-1273.712 – Placebo		Placebo – mRNA-1273.712	
	mRNA-1273.712	Placebo	Placebo	mRNA-1273.712
Leading to study discontinuation	0	0	0	0
AE of special interest (AESI)	1 (0.4)	1 (0.5)	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest.
Source: Table 14.3.1.2 and Table 14.3.1.3

Additional summaries of unsolicited AEs by subgroups are presented in Table 14.3.1.2.4, Table 14.3.1.2.5, Table 14.3.1.8.4, and Table 14.3.1.8.5. Unsolicited AEs in participants with elevated cTnI results are presented in Table 14.3.1.17.1, Table 14.3.1.17.2, Table 14.3.1.17.3, Table 14.3.1.17.4, and Table 14.3.1.17.5.

Deaths, SAEs, and Other Significant AEs

Deaths

No deaths were reported in Sequence 1 or Sequence 2 during this study.

Serious Adverse Events

Sequence 1 (mRNA-1273.712 – Placebo)

No SAEs were reported in Sequence 1.

Sequence 2 (Placebo – mRNA-1273.712)

In Sequence 2, an SAE of suicidal ideation was reported in a 14-year-old male participant on Day 20 after the mRNA-1273.712 injection. The participant had a history of major depressive disorder, attention deficit hyperactivity disorder, and cannabis use disorder. He was depressed due to the passing of his cousin, expressed thoughts of suicide to his parents, and was subsequently hospitalized. Treatment included guanfacine and the event resolved after 2 days. The Investigator assessed the event as not related to study injection.

AEs Leading to Discontinuation

Sequence 1 (mRNA-1273.712 – Placebo)

In Sequence 1, 1/500 (0.2%) participant had an AESI of seizure on Day 10 after the mRNA-1273.712 injection, which led to discontinuation of study injection. The event was assessed as not related to study injection by the Investigator.

Sequence 2 (Placebo – mRNA-1273.712)

In Sequence 2, 1/497 (0.2%) participant had 2 non-serious unsolicited AEs of urinary tract infection and rash on Day 15 after the placebo injection, both leading to discontinuation of study injection; the event of rash was reported as also leading to discontinuation from study participation. Both events were assessed as not related to study injection by the Investigator.

AESIs per Investigator Assessment

Sequence 1 (mRNA-1273.712 – Placebo)

In Sequence 1, AESIs were reported for 2 participants: 1 participant had an AESI of seizure on Day 10 following the mRNA-1273.712 injection, which led to discontinuation of study injection and 1 participant had an AESI of atrial fibrillation on Day 29 following the placebo injection; both events were moderate in severity and assessed as not related to study injection by the Investigator. These events are summarised below.

- Seizure: A 14-year-old male participant with a medical history of generalized tonic-clonic seizure that was not reported at the time of Screening, experienced a non-serious AESI of seizure (reported verbatim: worsening of generalized tonic clonic seizure [increased frequency]) on Day 10 after the mRNA-1273.712 injection, followed by another identical seizure 10 days later, on Day 20. Treatment for the seizures included levetiracetam and diazepam. Due to the event, the participant discontinued study injection and did not receive the second (placebo) injection. The event had not resolved (recovering/resolving) at the time of database lock.
- Atrial fibrillation: A 29-year-old male participant with a medical history of vaping, experienced a non- serious AESI of atrial fibrillation (reported verbatim: atrial fibrillation) on Relative Day 29 after the placebo injection. The participant underwent cardioversion approximately 1 week after the event, following which he continued to experience intermittent episodes of dyspnoea with exertion and transient fast heart rates. Treatment for the event included metoprolol and rivaroxaban. The event resolved with sequelae on Study Day 78 (Relative Day 38).

Sequence 2 (Placebo – mRNA-1273.712)

No AESIs were reported in Sequence 2.

Analyses of Unsolicited AEs by MedDRA Queries (SMQ and CMQ)

There were no events of myocarditis, pericarditis, and/or myopericarditis identified through review of the Cardiomyopathy and Non-infectious myocarditis/pericarditis SMQs or the CMQ for myocarditis and pericarditis.

Medically Attended Adverse Events

All of the unsolicited AEs reported in this study were MAAEs.

Clinical Laboratory Evaluation

No scheduled laboratory assessments for safety were 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.

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no notable changes or shifts from baseline in vital sign measurements.

Pregnancy

There were 3 participants who had a positive pregnancy test after receipt of study injection. The pregnancy outcome was elective abortion for 1 participant, and the pregnancy outcomes for the remaining 2 participants were still pending at the time of final database lock. Additional details for these pregnancies are available in the participant narratives (study P404 final CSR, section 15).

BIOMARKER EVALUATIONS

cTnI Levels

On Day 1 (prior to any study injection), there were 2/491 (0.4%) participants in Sequence 1 and 5/489 (1.0%) participants in Sequence 2 who had elevated cTnI.

Individual Participants with Elevated cTnI Levels

The prespecified primary and secondary analyses comparing the proportion of participants with elevated cTnI levels after receiving mRNA-1273.712 and placebo may not accurately reflect the effect of the study injections on cTnI levels, as they do not distinguish between new post-injection elevations and those already present at baseline. To address this potential limitation, longitudinal summaries of all cTnI values for individual participants with at least 1 cTnI elevation during the study were included and assessed in the context of temporally relevant physical activity data collected in the eDiary.

Overall, a total of 18 out of 981 participants in the Evaluable Set had at least 1 elevated cTnI result at any timepoint during the study (Table 5). Thus, most participants (>98%) in the Evaluable Set had normal cTnI levels throughout the study.

Table 5 Listing of Participants with Elevated cTnI at Any Timepoint by Injection Sequence

Participant ID	Age/Sex	Day 1 (pre-Inj 1)	Day 4	Day 29 (pre-Inj 2)	Day 32	Day 57 (EOS)	Elevated cTnI on Day 1 (pre-Inj 1)	Elevated cTnI after mRNA-1273.712 with no prior elevation	Elevated cTnI after placebo with no prior elevation	Relevant physical activity in eDiary
Sequence 1 (mRNA-1273.712 – Placebo)		← mRNA-1273.712 →								
				← placebo →						
[redacted]	12/F	<3	<3	<3	<3	85			Y	Y
	16/M	4	<3	4	<3	196			Y	Y
	17/F	39	27	19	20	22	Y			
	16/F	7	6	60	22	7		Y		
	14/M	183	1588	—	—	—	Y			Y
	22/M	8	26	11	19	380			Y	
Sequence 1 Total[a]		N=2	N=1	N=1	N=0	N=3	N=2	N=1	N=3	N=3
Sequence 2 (Placebo –mRNA-1273.712)		← placebo →								
				← mRNA-1273.712 →						
[redacted]	14/M	<3	8	<3	<3	144		Y		
	13/M	51	26	111	78	30			Y	
	19/F	105	27	50	46	10	Y			Y
	29/M	4	4	732	372	173			Y	Y
	12/F	481	13	<3	<3	<3	Y			Y
	17/F	41	48	34	33	42	Y			Y
	15/M	25	39	46	27	56		Y		Y
	28/F	32	25	41	43	23			Y	Y
	13/M	<3	<3	127	<3	<3			Y	Y
	26/M	<3	<3	2630	3492	390			Y	
	16/M	55	38	46	41	35	Y			
	16/M	116	68	45	157	45	Y			Y

Participant ID	Age/Sex	Day 1 (pre-Inj 1)	Day 4	Day 29 (pre-Inj 2)	Day 32	Day 57 (EOS)	Elevated cTnI on Day 1 (pre-Inj 1)	Elevated cTnI after mRNA-1273.712 with no prior elevation	Elevated cTnI after placebo with no prior elevation	Relevant physical activity in eDiary
Sequence 2 Total[a]		N=5	N=2	N=6	N=6	N=5	N=5	N=2	N=5	N=8

Abbreviations: cTnI = cardiac troponin I; eDiary = electronic diary; EOS = end of study; F = female; LLOQ = lower limit of quantification; M = male.

Note: All values were calculated using the units pg/mL. Elevated cTnI was defined as >53.53 pg/mL in males and >38.64 pg/mL in females. LLOQ=3 pg/mL for the cTnI assay. Note that physical activity collection in the eDiary did not encompass every type of activity.

[a] N is summarizing the total number of participants (per injection sequence) who had an elevated cTnI or had reported recent physical activity. Elevated cTnI levels for individual participants at each timepoint are indicated by bold font. Baseline cTnI levels at Day 1 (prior to any study injection) are shaded in purple. cTnI levels at Day 4/Day 32 (3 days after the mRNA-1273.712 injection) are shaded in yellow, and cTnI levels at Day 29/Day 57 (28 days after the mRNA-1273.712 injection) are shaded in orange. cTnI levels at Day 4/Day 32 (3 days after the placebo injection) are shaded in green, and cTnI levels at Day 29/Day 57 (28 days after the placebo injection) are shaded in blue.

Source: Listing 16.2.4.1, Listing 16.2.6.1, Listing 16.2.6.1.1, and Listing 16.2.6.2

Brief narratives for these participants are summarised below, except for the 2 participants () who did not report any physical activity data during the study.

Sequence 1 (mRNA-1273.712 – Placebo)

- A participant had elevated cTnI of 85 pg/mL at the Day 57 visit, 28 days after the placebo injection. The cTnI value was below LLOQ at all other timepoints. Physical activity (organized sports) was reported on the day of the Day 57 visit prior to the blood draw and on Day 2 (jog/run).
- A participant had elevated cTnI of 196 pg/mL at the Day 57 visit, 30 days after the placebo injection. The cTnI was 4 pg/mL at Day 1 and Day 29 prior to Injections 1 and 2, respectively, and below LLOQ at all other timepoints. Physical activity (lift weights) was reported on Days 2, 4, 25, 30, 32, 53, 55, 56, and on Day 57 prior to the blood draw.

- A participant had elevated cTnI of 39 pg/mL at the Day 1 visit prior to receiving any study injection. The cTnI remained detectable, but not in the elevated range, at all other timepoints. Physical activity (swim/water exercise) was reported on Days 25, 28, 55, 56, and 57.
- A participant had elevated cTnI of 60 pg/mL at the Day 29 visit, 28 days after the mRNA-1273.712 injection. The cTnI was detectable, but not in the elevated range, at all other timepoints including the Day 1 visit prior to receiving any study injection. Physical activity (organized sports) was reported on Days 1, 4, and 54.
- A participant had elevated cTnI of 183 pg/mL at the Day 1 visit prior to receiving any study injection. Three days after the mRNA-1273.712 injection, at the Day 4 visit, the cTnI was 1588 pg/mL. Physical activity (run/jog) was reported on Days 2 and 3, and the participant is known to be a cross-country runner. No additional study visits were conducted. All eDiary entries after Day 4 are missing. The site recorded a non-serious AE of abnormal ECG for this participant.
- A participant had elevated cTnI of 380 pg/mL at the Day 57 visit, 42 days after the placebo injection. The cTnI was detectable, but not in the elevated range, at all other timepoints including the Day 1 visit prior to receiving any study injection. Physical activity (organized sports) was reported on Days 1, 2, and 4.

Sequence 2 (Placebo – mRNA-1273.712)

- A participant had elevated cTnI of 144 pg/mL at the Day 57 visit, 31 days after the mRNA-1273.712 injection. The cTnI was 8 pg/mL at the Day 4 visit and was below LLOQ at all other timepoints. Physical activity (organized sports) was reported on Days 2 and 3.
- A participant had elevated cTnI of 111 pg/mL at the Day 29 visit prior to receiving the mRNA-1273.712 injection. Three days later, at the Day 32 visit, the cTnI was 78 pg/mL. The cTnI was detectable, but not in the elevated range, at all other timepoints. Physical activity (organized sports) was reported on Days 1 (before blood draw), 3, and 4. eDiary entries were missing from Days 25 through 53.
- A participant had elevated cTnI of 105 pg/mL at the Day 1 visit prior to receiving any study injection. At the Day 29 visit, the cTnI was 50 pg/mL prior to receiving the mRNA 1273.712 injection. Three days later, the cTnI was 46 pg/mL. The cTnI was detectable, but not in the elevated range, at all other timepoints. Physical activity (ride bicycle) was reported on Day 27. Most eDiary entries were missing.
- A participant had elevated cTnI of 732 pg/mL at the Day 29 visit prior to receiving the mRNA-1273.712 injection. Four days later, the cTnI was 372 pg/mL at the Day 32 visit. The cTnI was 173 pg/mL at the Day 57 visit. Physical activity (lift weights) was reported on Day 56. eDiary entries were missing from Days 25 through 28.
- A participant had elevated cTnI of 481 pg/mL at the Day 1 visit prior to receiving any study injection. Two days later, the cTnI was 13 pg/mL at the Day 4 visit after the placebo injection and below LLOQ at all other timepoints. Physical activity (jog/run) was reported on Days 1 (before blood draw), 2, 3, and 4. The remaining eDiary entries were missing.
- A participant had elevated cTnI of 41 pg/mL at Day 1 prior to receiving any study injection. Two days later, the cTnI was 48 pg/mL at the Day 4 visit after the placebo injection. The cTnI was detectable, but not in the elevated range, at the Day 29 and Day 32 visits, and was

elevated at 42 pg/mL, 30 days after the mRNA-1273.712 injection. Physical activity (swim/water exercise) was reported on Days 3, 4, 25, 26, 28, 30, 31, 32, 54, 55, and 57.

- A participant had elevated cTnI of 56 pg/mL at the Day 57 visit, 28 days after the mRNA-1273.712 injection. The cTnI was detectable, but not in the elevated range, at all other timepoints including Day 1 prior to receiving any study injection. Physical activity (organized sports or weightlifting) was reported on Days 2, 3, 4, 27, 29, and 53.
- A participant had elevated cTnI of 41 pg/mL at the Day 29 visit prior to receiving the mRNA-1273.712 injection. The cTnI was 43 pg/mL the next day. The cTnI was detectable, but not in the elevated range, at all other timepoints, including Day 1 prior to receiving any study injection. Physical activity (jog/run, ride bicycle, or heavy manual labour) was reported on Days 1, 3, 4, 28, 30, 31, 54, 55, and 56.
- A participant had elevated cTnI of 127 pg/mL at the Day 29 visit, 28 days after the placebo injection and prior to receiving the mRNA-1273.712 injection. The cTnI was below LLOQ at all other timepoints. Physical activity was reported at Days 25 (jog/run), 29 (organized sports), and 31 (jog/run and lift weights).
- A participant had elevated cTnI of 116 pg/mL at the Day 1 visit prior to receiving any study injection. The cTnI was 68 pg/mL at the Day 4 visit, 3 days after the placebo injection and was 157 pg/mL at the Day 32 visit, 3 days after the mRNA-1273.712 injection. The cTnI was detectable, but not in the elevated range, at Days 29 and 57. Physical activity (jog/run, organized sports, or heavy manual labour) was reported on Days 3, 25, 26, 27, 28, 30, 31, 54, 55, and 57.

Primary Endpoint

The primary endpoint in this study was the proportion of participants with elevated cTnI at Day 4 or Day 32 (3 days after Injection 1 or Injection 2).

On Day 4 or Day 32 (3 days after injection), there were 7/898 (0.8%) and 2/916 (0.2%) participants with elevated cTnI after the mRNA-1273.712 and placebo injections, respectively (Table 6). Out of the 9 total participants with elevated cTnI recorded 3 days after the study injection (mRNA-1273.712 or placebo), all but 1 participant in the mRNA-1273.712 injection group had elevated cTnI levels at the corresponding pre-Injection timepoint (Day 1 or Day 29). For the 1 participant in the mRNA-1273.712 injection group, although the cTnI level was within normal range at the pre-Injection timepoint (Day 29), the participant's cTnI levels had been elevated previously during the study at both Day 1 (pre-Injection) and Day 4 after the placebo injection.

Among the 7 participants with elevated cTnI 3 days after the mRNA-1273.712 injection, 4 participants had an increase in cTnI relative to the pre-injection values; all other cTnI values had actually decreased relative to the pre-injection values after the mRNA-1273.712 injection. In the 4 participants with increases, 1 participant had an elevated cTnI of 41 pg/mL (pre-injection) that was 43 pg/mL at Day 32, 1 participant had a cTnI of 45 pg/mL (pre-injection) that increased to 157 pg/mL at Day 32 (and subsequently decreased to 45 pg/mL by Day 57), and 1 participant had an elevated cTnI of 183 pg/mL (pre-injection) that increased to 1588 pg/mL at Day 4. Each of these participants had reported recent exercise in the eDiary. One additional participant who did not report any physical activity data during the study had an elevated cTnI of 2630 pg/mL (pre-injection) that increased to 3492 pg/mL at Day 32 (and had subsequently decreased to 390 pg/mL by Day 57).

There were no differences in the proportion of participants with elevated cTnI recorded 3 days after injection between the 2 injection groups (0.6% [95% CI: -0.1%, 1.4%]), and there were no increases from baseline (pre-injection) in the proportion of participants with elevated cTnI after the mRNA-1273.712 injection (-0.1% [95% CI: -0.6%, 0.4%]) or after the placebo injection (-0.4% [95% CI: -1.0%, 0.1%]) (Table 7). Participants with shifts in cTnI levels from baseline (pre-injection) to Day 4 and Day 32 (3 days after injection) are summarised in Table 7.

Assessor's comment:

Among the 7 subjects with elevated cTnI 3 days after the mRNA-1273.712 injection, 4 subjects had an increase in cTnI relative to the pre-injection values; all other cTnI values had actually decreased relative to the pre-injection values after the mRNA-1273.712 injection. Out of these 4 subjects 3 subjects reported recent physical activity which is known to increase cTnI levels. The remaining subject with already significant cTnI levels prior to vaccination had an additional increase of cTnI levels after vaccination but substantially decreased by D57. The reason for these changes in cTnI levels remains unknown as the subject did not report any physical activities in the eDiary. However, this subject is not present in the list of MAAEs (Safety Set, Listing 16.2.7.3) or in any AE listings in a document search by subject ID, indicating no symptoms associated with the increase of cTnI levels.

Overall, there were no differences in the proportion of participants with elevated cTnI recorded 3 days after injection between the 2 injection groups (0.6% [95% CI: -0.1%, 1.4%]), and there were no increases from baseline (pre-injection) in the proportion of participants with elevated cTnI after the mRNA-1273.712 injection (-0.1% [95% CI: -0.6%, 0.4%]) or after the placebo injection (-0.4% [95% CI: -1.0%, 0.1%]).

Secondary Endpoint

A secondary endpoint in this study was the proportion of participants with elevated cTnI at Day 29 or Day 57 (28 days after Injection 1 or Injection 2).

On Day 29 or Day 57 (28 days after injection), there were 6/865 (0.7%) and 9/859 (1.0%) participants with elevated cTnI after the mRNA-1273.712 and placebo injections, respectively (Table 8). Three of the 6 participants with elevated cTnI 28 days after the mRNA-1273.712 injection and 1 of the 9 participants with elevations 28 days after the placebo injection also had a cTnI elevation at a prior timepoint during the study.

There were no differences in the proportion of participants with elevated cTnI recorded 28 days after injection between the 2 injection groups (-0.4% [95% CI: -1.4%, 0.6%]), and there were no notable changes from baseline (pre-injection) in the proportion of participants with elevated cTnI after the mRNA-1273.712 injection (-0.1% [95% CI: -0.9%, 0.6%]) or after the placebo injection (0.3% [95% CI: 0.5%, 1.2%]).

Table 6 Participants with Elevated cTnI 3 Days After Injection by Injection Group (Evaluable Set)

	Injection Group	
	mRNA-1273.712[a] (N=938)	**Placebo[b] (N=942)**
Participants with non-missing cTnI at both pre-injection and 3 days after injection, N1	898	916
Participants with elevated cTnI at pre-injection, n (%)[c]	8 (0.9)	6 (0.7)
95% CI[d]	(0.4, 1.7)	(0.2, 1.4)
Participants with elevated cTnI at 3 days after injection, n (%)[c]	7 (0.8)	2 (0.2)
95% CI[d]	(0.3, 1.6)	(0.0, 0.8)
Difference, % (mRNA-1273.712 minus placebo)	0.6	
95% CI[e]	(-0.1, 1.4)	
Change in proportion of elevated cTnI from pre-injection to 3 days after injection, %	-0.1	-0.4
95% CI[f]	(-0.6, 0.4)	(-1.0, 0.1)

Abbreviations: CI = confidence interval; cTnI = cardiac troponin I.

Note: All values were calculated using the units pg/mL. Elevated cTnI was defined as >53.53 pg/mL in males and >38.64 pg/mL in females. LLOQ=3 pg/mL for the cTnI assay.

[a] The mRNA-1273.712 group was defined as participants who received mRNA-1273.712 for Injection 1 on Day 1 in the mRNA-1273.712 – placebo sequence (Sequence 1) and participants who received mRNA-1273.712 for Injection 2 on Day 29 in the placebo – mRNA-1273.712 sequence (Sequence 2).

[b] The placebo group was defined as participants who received placebo for Injection 1 on Day 1 in the placebo – mRNA-1273.712 sequence (Sequence 2) and participants who received placebo for Injection 2 on Day 29 in the mRNA-1273.712 – placebo sequence (Sequence 1).

[c] Percentages are based on N1.

[d] Calculated using the Clopper-Pearson method.

[e] Calculated using the Miettinen-Nurminen method.

[f] Changes in the proportion of elevated cTnI were calculated as the proportion of elevated cTnI at specified timepoint – proportion of elevated cTnI at Day 1 or Day 29 (pre-Injection 1 or pre-Injection 2) within each injection group. 95% CIs were calculated using the adjusted Wald interval for paired data, where the pre-injection and post-injection cTnI level from the same participant are paired.

Source: Table 14.2.1.1

Table 7 Participants with Shifts in cTnI Levels 3 Days After Injection by Injection Group (Evaluable Set)

	Injection Group	
	mRNA-1273.712[a] (N=938)	**Placebo[b] (N=942)**
Participants with ≥1 non-missing cTnI at Day 1 (pre-Injection 1) or Day 4 (after Injection 1), N2	491	490
Normal cTnI at both Day 1 (pre-Injection 1) and Day 4 (after Injection 1), n (%)[c]	477 (97.1)	473 (96.5)
Normal cTnI at Day 1 (pre-Injection 1) but elevated cTnI at Day 4 (after Injection 1), n (%)[c]	**0**	**0**
Normal cTnI at Day 1 (pre-Injection 1) and missing cTnI at Day 4 (after Injection 1), n (%)[c]	12 (2.4)	11 (2.2)
Elevated cTnI at both Day 1 (pre-Injection 1) and Day 4 (after Injection 1), n (%)[c]	**1 (0.2)**	**2 (0.4)**
Elevated cTnI at Day 1 (pre-Injection 1) but normal cTnI at Day 4 (after Injection 1), n (%)[c]	1 (0.2)	3 (0.6)
Elevated cTnI at Day 1 (pre-Injection 1) and missing cTnI at Day 4 (after Injection 1), n (%)[c]	0	0
Missing cTnI at Day 1 (pre-Injection 1) and normal cTnI at Day 4 (after Injection 1), n (%)[c]	0	1 (0.2)
Missing cTnI at Day 1 (pre-Injection 1) and elevated cTnI at Day 4 (after Injection 1), n (%)[c]	**0**	**0**
Participants with ≥1 non-missing cTnI at Day 29 (pre-Injection 2) or Day 32 (after Injection 2), N2	445	449
Normal cTnI at both Day 29 (pre-Injection 2) and Day 32 (after Injection 2), n (%)[c]	412 (92.6)	437 (97.3)
Normal cTnI at Day 29 (pre-Injection 2) but elevated cTnI at Day 32 (after Injection 2), n (%)[c]	**1 (0.2)**	**0**
Normal cTnI at Day 29 (pre-Injection 2) and missing cTnI at Day 32 (after Injection 2), n (%)[c]	23 (5.2)	10 (2.2)
Elevated cTnI at both Day 29 (pre-Injection 2) and Day 32 (after Injection 2), n (%)[c]	**5 (1.1)**	**0**
Elevated cTnI at Day 29 (pre-Injection 2) but normal cTnI at Day 32 (after Injection 2), n (%)[c]	1 (0.2)	1 (0.2)
Elevated cTnI at Day 29 (pre-Injection 2) and missing cTnI at Day 32 (after Injection 2), n (%)[c]	0	0
Missing cTnI at Day 29 (pre-Injection 2) and normal cTnI at Day 32 (after Injection 2), n (%)[c]	3 (0.7)	1 (0.2)
Missing cTnI at Day 29 (pre-Injection 2) and elevated cTnI at Day 32 (after Injection 2), n (%)[c]	**0**	**0**

Abbreviations: CI = confidence interval; cTnI = cardiac troponin I.

Note: All values were calculated using the units pg/mL. Elevated cTnI was defined as >53.53 pg/mL in males and >38.64 pg/mL in females. LLOQ=3 pg/mL for the cTnI assay.

[a] The mRNA-1273.712 group was defined as participants who received mRNA-1273.712 for Injection 1 on Day 1 in the mRNA-1273.712 – placebo sequence (Sequence 1) and participants who received mRNA-1273.712 for Injection 2 on Day 29 in the placebo – mRNA-1273.712 sequence (Sequence 2).

[b] The placebo group was defined as participants who received placebo for Injection 1 on Day 1 in the placebo – mRNA-1273.712 sequence (Sequence 2) and participants who received placebo for Injection 2 on Day 29 in the mRNA-1273.712 – placebo sequence (Sequence 1).

[c] Percentages are based on N2.

Source: Table 14.2.1.1

Table 8 Participants with Elevated cTnI 28 Days After Injection by Injection Group (Evaluable Set)

	Injection Group	
	mRNA-1273.712[a] (N=938)	Placebo[b] (N=942)
Participants with non-missing cTnI at both pre-injection and 28 days after injection, N1	865	859
Participants with elevated cTnI at pre-injection, n (%)[c]	7 (0.8)	6 (0.7)
95% CI[d]	(0.3, 1.7)	(0.3, 1.5)
Participants with elevated cTnI at 28 days after injection, n (%)[c]	6 (0.7)	9 (1.0)
95% CI[d]	(0.3, 1.5)	(0.5, 2.0)
Difference, % (mRNA-1273.712 minus placebo)	-0.4	
95% CI[e]	(-1.4, 0.6)	
Change in proportion of elevated cTnI from pre-injection to 28 days after injection, %	-0.1	0.3
95% CI[f]	(-0.9, 0.6)	(-0.5, 1.2)

Abbreviations: CI = confidence interval; cTnI = cardiac troponin I.

Note: All values were calculated using the units pg/mL. Elevated cTnI was defined as >53.53 pg/mL in males and >38.64 pg/mL in females. LLOQ=3 pg/mL for the cTnI assay.

[a] The mRNA-1273.712 group was defined as participants who received mRNA-1273.712 for Injection 1 on Day 1 in the mRNA-1273.712 – placebo sequence (Sequence 1) and participants who received mRNA-1273.712 for Injection 2 on Day 29 in the placebo – mRNA-1273.712 sequence (Sequence 2).

[b] The placebo group was defined as participants who received placebo for Injection 1 on Day 1 in the placebo – mRNA-1273.712 sequence (Sequence 2) and participants who received placebo for Injection 2 on Day 29 in the mRNA-1273.712 – placebo sequence (Sequence 1).

[c] Percentages are based on N1.

[d] Calculated using the Clopper-Pearson method.

[e] Calculated using the Miettinen-Nurminen method.

[f] Changes in the proportion of elevated cTnI were calculated as the proportion of elevated cTnI at specified timepoint – proportion of elevated cTnI at Day 1 or Day 29 (pre-Injection 1 or pre-Injection 2) within each injection group. 95% CIs were calculated using the adjusted Wald interval for paired data, where the pre-injection and post-injection cTnI level from the same participant are paired.

Source: Table 14.2.1.1

cTnI Levels by Subgroups

There were no notable differences in the proportion of participants with elevated cTnI results in the injection groups when summarised by age group or sex. The proportion of elevated cTnI results was generally higher in males compared with females within both injection groups (Table 9).

Table 9 Participants with Elevated cTnI by Injection Group and Subgroups (Evaluable Set)

	Injection Group	
	mRNA-1273.712[a] n/N1 (%)	Placebo[b] n/N1 (%)
12 to 17 years	**N=429**	**N=435**
Participants with elevated cTnI at 3 days after injection[c]	3/415 (0.7)	2/424 (0.5)
Participants with elevated cTnI at 28 days after injection[c]	4/406 (1.0)	4/398 (1.0)
18 to 30 years	**N=509**	**N=507**
Participants with elevated cTnI at 3 days after injection[c]	4/483 (0.8)	0/492 (0)
Participants with elevated cTnI at 28 days after injection[c]	2/459 (0.4)	5/461 (1.1)
Female	**N=502**	**N=507**
Participants with elevated cTnI at 3 days after injection[c]	2/478 (0.4)	1/492 (0.2)
Participants with elevated cTnI at 28 days after injection[c]	2/458 (0.4)	3/462 (0.6)
Male	**N=436**	**N=435**
Participants with elevated cTnI at 3 days after injection[c]	5/420 (1.2)	1/424 (0.2)
Participants with elevated cTnI at 28 days after injection[c]	4/407 (1.0)	6/397 (1.5)

Abbreviation: cTnI = cardiac troponin I.

Note: All values were calculated using the units pg/mL. Elevated cTnI was defined as >53.53 pg/mL in males and >38.64 pg/mL in females. LLOQ=3 pg/mL for cTnI assay.

N=Number of participants in the Evaluable Set. N1=Number of participants with non-missing cTnI at both pre-injection and the corresponding timepoint.

[a] The mRNA-1273.712 group was defined as participants who received mRNA-1273.712 for Injection 1 on Day 1 in the mRNA-1273.712 – placebo sequence (Sequence 1) and participants who received mRNA-1273.712 for Injection 2 on Day 29 in the placebo – mRNA-1273.712 sequence (Sequence 2).

[b] The placebo group was defined as participants who received placebo for Injection 1 on Day 1 in the placebo – mRNA-1273.712 sequence (Sequence 2) and participants who received placebo for Injection 2 on Day 29 in the mRNA-1273.712 – placebo sequence (Sequence 1).

[c] Percentages are based on N1 (the number of participants with non-missing cTnI at both pre-injection and post-injection [3 or 28 days after injection]).

Source: Table 14.2.1.2 and Table 14.2.1.3

2.3.3. Discussion on clinical aspects

The MAH submitted study mRNA-1273-P404 as part of the post-authorisation measure which is investigating the influence of vaccination with mRNA-1273.712 (Omicron KP.2 monovalent) on the elevation of cardiac troponin I (cTnI) levels. cTnI is used as a biomarker used to measure myocardial injury while it is also known that physical exercise may result in the elevation of cTnI levels. Therefore, an eDiary was used to monitor physical activities of the participants which is considered appropriate.

The submitted Phase 4 randomised, placebo-controlled, crossover study was conducted in the United States between October 2024 and January 2025. Approximately 1000 participants were planned to be enrolled and randomised in a 1:1 ratio (approximately 500 participants in each injection sequence) to receive 2 study injections (mRNA-1273.712 and placebo) in a crossover design. The design of study P404 allows to compare levels of cTnI prior to and after vaccination versus placebo. Spikevax mRNA-1273.712 was approved by the US FDA in the United States (US) during study conduct.

Overall, the Inclusion and Exclusion criteria are reasonable in order to investigate the effect of vaccination with Spikevax on the elevation of cTnI in subjects with a reduced risk of elevated cTnI.

Study P404 enrolled approximately 1000 subjects in total. With the observed rate of myocarditis/pericarditis of <1 in 10 000 doses administered it cannot be expected that events of myocarditis/pericarditis are observed in this study. A study that is meant to detect cases of myocarditis/pericarditis is not feasible due to the large number of subjects. The information that can be gathered from this study is whether there is an elevation of cTnI after vaccination with

mRNA.1273.712 indicative for myocardial injury. Applying the CDC case definition for probable or confirmed myocarditis, pericarditis, and myopericarditis events is acceptable for the purpose of the study. Furthermore, use of the Atellica IM High-sensitivity Troponin I assay is appropriate for the purpose of this study. Demographics for subjects included in this study were balanced and appropriate.

Safety assessments were based on the unsolicited AEs collected in this study including SAEs, MAAEs, AESIs, and AEs leading to withdrawal of study injection and/or study participation, as well as vital sign measurements and physical examination findings.

In summary, there were no deaths, SAEs or AEs assessed as related to study intervention which is acknowledged. Unsolicited AEs did not result in a new safety signal. AEs of special interest were searched by investigator reported AESIs and by programmed SMQs and supplemental CMQs which is acknowledged. Expectedly, there were no cases of myocarditis or pericarditis identified.

A total of 18 out of 981 participants in the Evaluable Set had at least 1 elevated cTnI result at any timepoint during the study. 11 of them were part of the placebo part of the study and none of the 18 participants with elevated cTnI reported signs, symptoms, or AEs consistent with myocarditis or pericarditis.

Among the 7 subjects with elevated cTnI 3 days after the mRNA-1273.712 injection, 4 subjects had an increase in cTnI relative to the pre-injection values; all other cTnI values had actually decreased relative to the pre-injection values after the mRNA-1273.712 injection. Out of the 4 subjects 3 subjects reported recent physical activity which is known to increase cTnI levels. The remaining subject with already significant cTnI levels prior to vaccination had an additional increase of cTnI levels after vaccination but substantially decreased by D57. The reason for these changes in cTnI levels remains unknown as the subject did not report any physical activities in the eDiary. However, this subject is not present in the list of MAAEs (Safety Set, Listing 16.2.7.3) or in any AE listings in a document search by subject ID, indicating no symptoms associated with the increase of cTnI levels.

Overall, there were no differences in the proportion of participants with elevated cTnI recorded 3 days after injection between the 2 injection groups (0.6% [95% CI: -0.1%, 1.4%]), and there were no increases from baseline (pre-injection) in the proportion of participants with elevated cTnI after the mRNA-1273.712 injection (-0.1% [95% CI: -0.6%, 0.4%]) or after the placebo injection (-0.4% [95% CI: -1.0%, 0.1%]).

3. CHMP overall conclusion and recommendation

The MAH submitted study mRNA-1273-P404 as part of the post-authorisation measure which was investigating the influence of vaccination with mRNA-1273.712 (Omicron KP.2 monovalent) on the elevation of cardiac troponin I (cTnI) levels as a measure for myocardial injury.

Overall, there were no differences in the proportion of participants with elevated cTnI recorded 3 days after injection between the 2 injection groups (0.6% [95% CI: -0.1%, 1.4%]), and there were no increases from baseline (pre-injection) in the proportion of participants with elevated cTnI after the mRNA-1273.712 injection (-0.1% [95% CI: -0.6%, 0.4%]) or after the placebo injection (-0.4% [95% CI: -1.0%, 0.1%]).

Therefore, based on the number of 1000 participants, vaccination with mRNA.1273 and its derivatives **is not strongly associated** with an increase in cTnI levels indicative for myocardial injury.

☒ **Fulfilled:**

No regulatory action required.