CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age
Protocol Number:	mRNA-1073-P101
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number:	IND: 28200
Amendment Number	2
Date of Amendment 2	16 Aug 2022
Date of Original Protocol:	04 Nov 2021

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age
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Protocol accepted and approved by:

See eSignature and date at the end of the document

PPD	Date

ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: PPD
e-mail:
PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age" dated 16 Aug 2022 and the most recent version of the Investigator's Brochure.

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

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

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

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	16 Aug 2022
Amendment 1	25 Feb 2022
Original Protocol	04 Nov 2021

Amendment 2, 16 Aug 2022: Current Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment:

The purpose of this amendment is to remove the Phase 2 expansion part of this study, which is now planned as part of a future Phase 2/3 trial. As originally planned, the Sponsor will use safety and immunogenicity data from the ~550 participants to select a dose level for Phase 2/3. The Phase 2 expansion part was initially planned to provide additional safety data with potential immunogenicity assessment at a later time. The Sponsor considers the data from 550 participants in mRNA-1073-P101, 729 participants who received mRNA-1010 in Study mRNA-1010-P101, approximately 1700 participants who received mRNA-1010 in Study mRNA-1010-P301 (as of 16 Aug 2022), and an estimated total of 661,128,345 doses of mRNA-1273 administered (as of 15 Jun 2022) to be supportive of advancement to Phase 2/3. The final analysis of all endpoints will be performed after all participants in the revised Phase 1/2 study have completed Day 181/End of Study (EoS).

The summary of changes table provided below describes the major changes made in Amendment 2 compared to Amendment 1, including the sections modified and the corresponding rationales. As applicable, the synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes From Protocol Amendment 1 to Protocol Amendment 2

Section # and Name	Description of Change	Brief Rationale
Global	• Deleted wording relevant to the Phase 2 portion of the study. • Decreased the total number of participants from 1050 to 550.	• The Sponsor will use safety and immunogenicity data from the 550 participants to select a dose level for the Phase 2/3 study.
Sections 1.1. (Synopsis), 2.1.(Background and Overview)	• Updated information of COVID-19 cases and deaths as of 19 Apr 2022.	• To update latest information in support to this study.

Section # and Name	Description of Change	Brief Rationale
Sections 1.1. (Synopsis), 2.1.1 (mRNA-1010), 2.2.2 (Clinical Studies)	• Modified text for background information on Phase 3 program for this vaccine and development of mRNA-1010 studies.	• To update latest information in support to this study.
Sections 1.1. (Synopsis), 5.2. (Exclusion Criteria)	• To Exclusion Criterion #9, added: "Inhaled, nasal, and topical steroids are not exclusionary."	• To clarify that inhaled, nasal, and topical steroids are not considered systemic agents and potential participants who have received inhaled, nasal, and topical steroids do not meet Exclusion Criterion #9.
Sections 1.1 (Synopsis), 9.4. (Analysis Set)	• Replaced "and have no major protocol deviations that impact the immune response" with "do not have influenza or SARS-CoV-2 infection at baseline and post-baseline up to Day 29 (as documented by positive RT-PCR testing result) and have no major protocol deviations and/or prohibited concomitant medication use (documented in the Section 6.5.3.) that are prespecified with impacts on the immune response and should be excluded from the PP set."	• Specifying criteria for PP set.
Sections 1.1 (Synopsis), 4.1. (General Design), 9.6. (Planned Analysis), 9.6.1. (Interim Analysis)	• Deleted description of the second interim analysis (IA2). • Clarified that one IA will be performed after the first 50 participants in Group 1 and 100 participants each in Groups 2, 3, 4, 5, and 6 have completed their Day 29 visit assessments and will include the safety and immunogenicity data collected up to Day 29.	• IA2 was scheduled to be performed on the data from participants in the Phase 2 expansion phase which will not occur.
Sections 1.1 (Synopsis), 4.4. (End of Study Definition), 9.6.2. (Final Analyses)	• Clarified that the final analysis will occur after 550 participants in Phase 1 have completed Day 181/EoS.	• The expansion of the Phase 2 part of the study will not occur. The study will be closed after the 550 participants complete Day 181/EoS.
Section 4.3. (Choice of Vaccine Doses)	• Updated mRNA-1273 booster guidance for older people and for certain immunocompromised individuals.	• The FDA recently amended the emergency use authorization to authorize a second booster dose for people 50 years of age and

Section # and Name	Description of Change	Brief Rationale
		older and for certain immunocompromised individuals.
Section 6.5.3. (Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant From Per-Protocol Analyses)	• Added: "Antiviral and antiretroviral medications."	• Antiviral and antiretroviral medications interfere with SARS-CoV-2 immunologic assays used in this study; participants using either may be excluded from PP analysis.
Section 7.1.1.1. (Pause Rules Based on the Occurrence of a Single Event and Adjudicated by the Data and Safety Monitoring Board)	• Replaced "Any" With "A" in Pause Rule 3: A systemic immediate hypersensitivity reaction within 60 minutes after the study vaccination[2] • Added footnote 2: "Systemic immediate hypersensitivity reaction refers to anaphylaxis as defined in Section 8.4.7.1."	• To clarify that a systemic immediate hypersensitivity reaction should only trigger a pause if the reaction meets the definition of anaphylaxis as stated in Section 8.4.7.1: Anaphylaxis.
Section 7.1.1.2. (Pause Rules Based on the Occurrence of Events in a Proportion of Participants)	• Added "exposed" to clarify instructions for calculating pause rules based on the occurrence of events in a proportion of participants. • Updated level heading to Section 7.1.2	• For the first 9 participants in each vaccination group (initial stage), the pause rule will be considered to be met if 2 of the first 9 participants experience the same solicited AR or the same MedDRA preferred term unsolicited AE or laboratory abnormality. Following the initial stage, the calculation for ≥ 20% of participants includes exposed participants in the initial stage and the expansion stage as the total number of participants in the denominator.
Section 7.1.1.2. (Pause Rules Based on the Occurrence of Events in a Proportion of Participants)	• Added: "(specified in Section 8.1.5.)." • Updated level heading to Section 7.1.2	• Clarifying PP laboratory assessments relevant to Pause Rule 7
Section 8. (Study Assessments)	• Deleted statement that the Screening Visit and Day 1 visit may be completed on the same day for Phase 2.	• The expansion of the Phase 2 part of the study will not occur.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.8. (Assessment for Respiratory Viral Infection)	• Replaced "respiratory symptoms" with "symptoms consistent with protocol-defined ILI (Section 8.4.5.) or COVID-19 (Section 8.4.6.)."	• Clarified symptoms during the 7-day period after vaccination that should trigger evaluation for COVID-19 and influenza.
Section 8.2. (Immunogenicity Assessments)	• Deleted language stating that blood samples from Phase 2 participants will be collected.	• The expansion of the Phase 2 part of the study will not occur.
Section 8.4.1. (Adverse Event)	• Added: "An incidental, asymptomatic RT-PCR confirmed COVID-19 case (ie, workplace screening) should be reported as an unsolicited AE of "asymptomatic COVID-19" if occurring during the first 28 days post study vaccination unless the RT-PCR test was performed on the NP swab collected prior to study vaccination (Day 1)."	• To clarify that asymptomatic COVID-19 detected prior to vaccination should not be reported as an unsolicited AE.
Section 9.5.3. (Immunogenicity Analysis)	• Added: "Between-group comparisons will be evaluated in terms of immunogenicity endpoints (GMR and SCR/SRR difference) in the PP set and will be specified in the SAP in greater detail."	• Clarifying immunogenicity analysis.
Section 9.5.5. (Subgroup Analyses)	• Deleted text "or previous COVID-19 vaccine type-specific."	• Updated to remove Phase 2 related analysis.
Section 11.1.5. (Recruitment Procedures)	• Updated title to "Recruitment Strategy" and text added: "Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate. Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site."	• This update is to align with EU-CTR.

Section # and Name	Description of Change	Brief Rationale
Section 11.1.9. (Data Protection)	• Confidentiality information updated to add: "The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access."	• This update is to align with EU-CTR.
Section 11.3 (Appendix 3)	• Updated: Renamed the "Additional Notes" column as "Medical Concept Descriptions/Guidance" and updated the contents in that column.	• To provide the most updated description of medical concepts of interest in COVID-19 vaccine safety surveillance, which should be reported as AESI(s).
Table of Contents	• Collapsed Pause Rules into Sections 7.1, 7.1.1. and 7.1.2. • Deleted Table 2 "Schedule of Events Phase 2." • Deleted "Phase 1" from Table 5 and Table 6. • Deleted Table 7 "Phase 2 Pause Rule Criteria Events and Thresholds Single Event."	• Changes to Table of Contents are consistent with relevant changes to the study described above.

Abbreviations: AESI = adverse event of special interest; AE = adverse event; COVID-19 = coronavirus disease 2019; DSMB = data safety monitoring board; eCRF = electronic case report form; EoS = end of study; EU-CTR = European Union Clinical Trials Regulation; FDA = Food and Drug Administration; GMR = geometric mean ratio; IA = interim analysis; ILI = influenza-like illness; IST = internal safety team; MAAE = medically attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NP = nasopharyngeal swab; PP = per-protocol; RT-PCR = reverse transcriptase polymerase chain reaction; SAP = statistical analysis plan; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate.

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:	ModernaTX, Inc.
Name of Investigational Product:	mRNA-1073
Protocol Title:	Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age
Protocol Number:	mRNA-1073-P101, Amendment 2
Study Duration:	Approximately 7 months Study participants will be screened up to 28 days prior to randomization and vaccination and followed for 6 months after intramuscular (IM) administration of investigational product (IP)
Phase of Development:	Phase 1/2
Estimated Date First Participant Enrolled:	May 2022
Estimated Date Last Participant Completed:	December 2022
Proposed Country:	Approximately 15 sites in the United States

Background and Rationale for Study:

ModernaTX, Inc. (the Sponsor) is developing mRNA-1073, a custom manufactured lipid-encapsulated messenger RNA (mRNA)-based prophylactic vaccine encoding for antigens from influenza viruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). mRNA-1073 encodes for the respective antigens also encoded for by mRNA-1010 and mRNA-1273 (also known as Moderna coronavirus disease 2019 [COVID-19] vaccine).

Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year resulting in a severe challenge to public health. Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the Northern Hemisphere (NH) and Southern Hemisphere (SH). Because influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO. Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice per year (once for the NH and once for the SH). Influenza A and influenza B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages).

Currently, licensed seasonal influenza virus vaccines rarely exceed 50% overall effectiveness and are poorly effective during years when the circulating viruses do not match the strains selected for the vaccine antigens. Influenza vaccines based on mRNA technology could provide several benefits compared to current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, as well as improved protection in older adults.

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome. An outbreak of a novel CoV (later designated SARS-CoV-2, the causative agent of COVID-19) initially emerged in Wuhan, Hubei Province, China in December 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020, and COVID-19 continues to have a major global public health impact, with more than 500 million cases and 6.2 million deaths as of 19 Apr 2022.

The Sponsor has developed a rapid-response, proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The

delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently.

The Sponsor is using its mRNA-based platform to develop a custom manufactured lipid nanoparticle-encapsulated, mRNA-based vaccine against diseases caused by influenza virus types A and B. The proposed development candidate mRNA-1010 is a quadrivalent vaccine containing mRNAs that encode for the hemagglutinins (HAs) of the 4 strains recommended by the WHO for cell- or recombinant-based vaccines. Equal amounts of mRNAs that encode for membrane-bound wild-type versions of each of the 4 different strains will be used for the HA components. The mRNA-1010 development candidate will be administered as a single intramuscular (IM) injection and aims to elicit protection from all seasonal influenza viruses covered by the vaccine. The Sponsor is conducting a first-in-human (FIH) Phase 1/2 study of mRNA-1010 (NCT04956575), a seasonal influenza vaccine, to establish preliminary safety, reactogenicity, and immunogenicity data that has supported the initiation of a Phase 3 program for this vaccine (NCT05415462).

mRNA-1273 encodes for the full-length S protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S-2P) in a prefusion conformation. The CoV-S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAbs) that prevent infection. It has been confirmed that the stabilized SARS-CoV-2 S-2P antigen presents in the correct prefusion conformation. In December 2020, mRNA-1273 was granted Emergency Use Authorization (EUA) in the US for the prevention of COVID-19 for individuals 18 years of age and older. In November 2021, the US Food and Drug Administration (FDA) granted EUA for an mRNA-1273 booster dose (CCI) to be given at least 5 months after the primary series with mRNA-1273 in adults aged 18 years and older. In August 2021, the Sponsor filed a Biologics License Application (BLA) with the FDA for the full licensure of the mRNA-1273 vaccine for active immunization to prevent COVID-19 in individuals 18 years of age and older. In January 2022, the US FDA approved the BLA for SPIKEVAX (mRNA-1273) to prevent COVID-19 in individuals 18 years of age and older.

mRNA-1073 is a custom manufactured lipid-encapsulated mRNA-based prophylactic vaccine encoding for antigens from influenza viruses and SARS-CoV-2.

The administration of mRNA-1073 vaccine, encoding for the respective antigens also encoded for by mRNA-1010 (seasonal influenza) and mRNA-1273 (SARS-CoV-2), has the potential to efficiently reduce the overall burden of acute viral respiratory diseases by providing simultaneous protection against influenza and SARS-CoV-2 viruses in a convenient dosing regimen. mRNA-1073 offers greater convenience and has the potential to lead to increased compliance with vaccine recommendations, which has been frequently utilized for pediatric

vaccines. Furthermore, this combined regimen could provide a public health benefit through synergistically increasing coverage rates against influenza and SARS-CoV-2 viruses.

This Phase 1/2 study will collect safety and immunogenicity data to further inform the clinical development of mRNA-1073.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of study vaccines	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period post vaccination • Frequency and severity of any unsolicited AEs during the 28-day follow-up period post vaccination • Frequency of any SAEs, AESIs, MAAEs, and AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
• To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 across study vaccine arms at Day 29	• GMT and GMFR at Day 29 compared with Day 1 (baseline) by HAI assay for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer ≥ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is ≥ 1:10 in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥ 4-fold if baseline is ≥ LLOQ or ≥ 4 × LLOQ if baseline titer is < LLOQ in nAb titers measured by PsVNA (or binding antibody assay).
• To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 at all evaluable humoral immunogenicity time points	• GMT and GMFR compared with Day 1 (baseline) by HAI for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2 • Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) as defined above
Exploratory (may be performed)	

• To evaluate the humoral immunogenicity against vaccine mismatched strains	• GMT and GMFR (compared to Day 1) to vaccine mismatched strains
• To evaluate the humoral immunogenicity against vaccine-matched and mismatched strains using alternative methods	• GMT and GMFR (compared to Day 1) to vaccine-matched and mismatched strains assayed by alternative methods (eg, microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2)
• To evaluate cellular immunogenicity in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells and T cells after vaccination
• To further characterize the immune response across study vaccines	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
• To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates	• Frequency of laboratory-confirmed clinical influenza and COVID-19 and assessment of immune responses to infection and viral isolates

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Overall Study Design:

This is a Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 compared to co-administered mRNA-1010 and mRNA-1273 vaccines and to the individual vaccines alone in healthy adults 18 to 75 years of age.

Participants in the study will participate in a Screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and a follow-up period (up to 6 months after vaccination).

On Day 1, each participant will receive 2 injections administered IM, one in each arm, in the deltoid muscle. The vaccines to be tested include: 1) mRNA-1273 vaccine encoding for the full-length S protein of SARS-CoV-2, modified to introduce S-2P in a prefusion conformation; 2) mRNA-1010 vaccine encoding for the HA surface glycoproteins of the 4 strains by the WHO for the 2022 SH influenza season cell- or recombinant-based vaccines; and 3) mRNA-

1073 vaccine encoding for the respective antigens also encoded for by mRNA-1010 and mRNA-1273. The placebo and the diluent for mRNA-1073 vaccine will be 0.9% sodium chloride (normal commercial saline) injection, which meets the criteria of the US Pharmacopeia (USP).

The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine (primary series or booster) must be ≥ 120 days prior (or less per local guidance) to the randomization visit. Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have no known history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening. Randomization will be stratified by age (18 to 49 years old and 50 to 75 years old, balanced across the 2 age groups within each vaccination group). The numbers of participants and groups are shown in the below table.

Participants will have 6 visits and 4 safety phone calls. Vaccines (mRNA-1073, mRNA-1010, or mRNA-1273) and placebo (as indicated) will be administered as IM injections, one in each arm, in the deltoid muscle. Safety and/or immunogenicity and/or biomarkers study visits will occur on Days 4, 8, 29, and 181 (end of study [EoS]). Study visits will include scheduled safety phone calls at Days 57, 91, 121, and 151 to collect adverse events (AEs), medically attended AEs (MAAEs), AEs of special interest (AESIs), AEs leading to withdrawal, serious adverse events (SAEs), and information about concomitant medications and receipt of non-study vaccinations.

Study Arms

#	Group Name	Sample Size (N=550)
1	mRNA-1273 CCI + placebo	50
2	mRNA-1010 + placebo	100
3	mRNA-1010 + mRNA-1273 CCI co-administration	100
4	mRNA-1073 CCI + placebo	100
5	mRNA-1073 placebo	100
6	mRNA-1073 placebo	100

Safety Oversight:

An internal safety team, inclusive of, at a minimum, the Sponsor's medical monitor, Sponsor's safety physician, and a contract research organization (CRO) medical monitor, will be formed

to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the data safety monitoring board (DSMB). The internal safety team (IST) will conduct a scheduled review of safety data after at least 55 participants (approximately 5 participants in Group 1 and approximately 10 participants in Groups 2 to 6) have completed the Day 8 visit. Enrollment will be ongoing while this review is conducted if no pause rules have been met and the study team has not identified any safety concerns. The IST will also conduct ad hoc reviews as requested by the study medical monitor and the study team.

The DSMB, composed of external/independent subject matter experts, will conduct scheduled unblinded reviews of safety data and as needed if any pause rule is met or as otherwise requested by the study team and/or IST as described in the DSMB charter.

An independent Cardiac Event Adjudication Committee (CEAC) that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

Study Population:

Number of Participants: Approximately 550 participants

Target Population: Healthy adults 18 to 75 years old

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adults 18 to 75 years of age at the time of consent (Screening Visit).
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.

4. Body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2 (inclusive) at the Screening Visit.
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized. A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.
6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
   - Has a negative pregnancy test at the Screening Visit and on the day of vaccination (Day 1).
   - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
   - Has agreed to continue adequate contraception through 3 months following vaccine administration. Adequate female contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label.
   - Is not currently breastfeeding.
7. Participants must have been fully vaccinated for COVID-19 primary series according to the locally authorized or approved regimen, and their last COVID-19 vaccine (primary series or booster) was ≥ 120 days prior to the randomization visit (or less per local guidance).

Exclusion Criteria:

Participants meeting any of the following criteria at the Screening Visit, unless noted otherwise, will be excluded from the study:

1. Participant is acutely ill or febrile (temperature ≥ 38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
2. Participant has a history of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication ≤ 60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the investigator.

3. Participant has a reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease.
4. Participant has dermatologic conditions that could affect local solicited adverse reaction (AR) assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Participant has a reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA vaccine(s) or any components of the mRNA vaccines.
6. Participant has a reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. Participant has a diagnosis of malignancy within previous 10 years (excluding nonmelanoma skin cancer).
8. Participant has any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
9. Participant has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 10 mg/day of prednisone or equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are not exclusionary.
10. Participant has received or plans to receive any vaccine authorized or approved by a local health agency ≤ 28 days prior to study injections (Day 1) or plans to receive a vaccine authorized or approved by a local health agency within 28 days before or after the study injections.
11. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine ≤ 180 days prior to the randomization visit.

12. Participant has tested positive for influenza by local health authority approved testing methods ≤ 180 days prior to the Screening Visit.
13. Participant has had close contact to someone with SARS-CoV-2 infection or COVID-19 as defined by the US CDC in the past 10 days prior to the Screening Visit.
14. Participant has known history of SARS-CoV-2 infection within ≤ 90 days.
15. Participant has received systemic immunoglobulins or blood products ≤ 90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study.
16. Participant has a history of myocarditis, pericarditis, or myopericarditis.
17. Participant has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
18. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
19. Participant is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.
20. Participant has clinical screening laboratory values (total white blood cell count, hemoglobin, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, and total bilirubin) > Grade 1.

Treatments:

Study Intervention:	mRNA-1073 is administered as a single dose and aims to elicit protection from influenza and SARS-CoV-2. mRNA-1073 contains mRNA coding for 4 HA antigens of the influenza virus strains recommended for the 2022 SH seasonal vaccines by the WHO and the mRNA for the S protein of SARS-CoV-2 virus formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG-2000-DMG). mRNA-1073 is based on the antigens encoded for by mRNA-1010 and mRNA-1273 and is

	intended as a single annual dose for protection from seasonal influenza and SARS-CoV-2. Commercially available 0.9% sodium chloride, USP will be used as appropriate for dose preparation. mRNA-1010 is administered as a single dose and aims to elicit protection from influenza A and B viruses. mRNA-1010 is a quadrivalent vaccine containing mRNAs encoding for the HAs of the 4 strains recommended by the WHO for 2022 SH cell- or recombinant-based vaccines formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG-2000-DMG. Equal amounts of mRNAs encoding for each of the 4 different strains are used for the HA components. mRNA-1010 is administered as a single dose and aims to elicit protection from all seasonal influenza viruses covered by the vaccine. mRNA-1273 is administered as a single dose and aims to elicit protection from SARS-CoV-2. mRNA-1273 contains mRNA CX-024414 encoding for the S-2P of Wuhan-Hu-1. mRNA-1273 consists of the mRNA formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG-2000-DMG.
Dose/Route/ Schedule:	mRNA-1073, mRNA-1010, or mRNA-1273 and placebo (if indicated) will be administered as IM injections, one in each deltoid muscle on Day 1, according to the procedures specified in the Pharmacy Manual. Each arm (left and right) and the corresponding vaccine or placebo administered will be recorded by the unblinded site staff and will be kept confidential from other study documents/personnel before unblinding is authorized.

Procedures and Assessments:

Safety Assessments:

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

- Solicited local and systemic ARs that occur during the 7 days following vaccine administration (ie, the day of study injections [Day 1] and 6 subsequent days). Solicited ARs will be recorded daily using electronic diaries. Local solicited ARs will be recorded separately for each injection site.
- Unsolicited AEs observed or reported during the 28 days following vaccination (ie, the day of injection [Day 1] and 27 subsequent days).
- SAEs, AESIs, MAAEs, and AEs leading to discontinuation from study participation from vaccination on Day 1 through Day 181/EoS or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Symptom Reporting electronic diary (eDiary) for influenza-like illness (ILI) and COVID-19 from Day 1 through Day 181/EoS as described under assessment for respiratory viral infection.
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

The incidence and severity of the above events will be monitored by an IST as per the charter.

Immunogenicity Assessments:

Blood samples for immunogenicity assessments will be collected per the schedule of events. The following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay
- Influenza: Serum nAb level as measured by microneutralization assay as potential substitution to the HAI assay
- SARS-CoV-2: Serum nAb titers as measured by pseudovirus neutralization assay (PsVNA) assay and potentially serum binding antibody titers by enzyme-linked immunosorbent assay (ELISA) or multiplex assay specific to the SARS-CoV-2 proteins.
- Cellular immunogenicity in a subset of participants

Assessment for Respiratory Viral Infection:

During the study, participants might experience symptoms consistent with ILI or SARS-CoV-2 infection. All participants will provide nasopharyngeal (NP) swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV 2, as influenza or COVID-19 symptoms may confound reactogenicity assessments. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Efficacy Assessments:

While the study will not be powered for efficacy assessments, symptoms of infection with respiratory pathogens will be tracked as an exploratory objective in this study.

Sample Size:

The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different study groups.

The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine must be ≥ 120 days prior to the randomization visit (or less per local guidance). Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have not had known history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening.

Approximately 550 participants will be enrolled at a CCI [redacted]. A sample size of 100 participants in one group has at least an 85% (or 95%) probability to observe at least 1 participant with an AE at a true 2% (or 3%) AE rate (see table below).

Randomized Sample Size Calculations

Sample Size	True AE Rate	Probability to Observe 0 AEs	Power to Detect at Least 1 AE
50	0.05	7.7%	92.3%
50	0.03	21.8%	78.2%
100	0.03	4.8%	95.2%
100	0.02	13.3%	86.7%

Abbreviation: AE = adverse event.

Analysis Sets:

Set	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.

FAS[1]	The FAS consists of all randomly assigned participants who receive the IP.
PP Set[2]	The PP set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment, do not have influenza or SARS-CoV-2 infection at baseline and post-baseline up to Day 29 (as documented by positive RT-PCR testing result), and have no major protocol deviations and/or prohibited concomitant medication use (documented in Section 6.5.3) that are prespecified with impacts on the immune response and should be excluded from the PP set.
Safety Set[3]	The safety set consists of all randomly assigned participants who receive the IP.
Solicited Safety Set[4]	The solicited safety set consists of all participants in the safety set who contribute any solicited AR data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; PP = per-protocol.
[1] For the FAS, participants will be analyzed according to the group to which they were randomized.
[2] The PP set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.
[3] The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the vaccination group corresponding to what they actually received.
[4] The solicited safety set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to what they actually received.

Safety Analyses:

All safety analyses are descriptive in nature and will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by study arm. Participants will be included in the vaccination group corresponding to what they actually received. Local solicited reactogenicity analysis will be presented by study group and for each injection content, respectively.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs); unsolicited AEs (including any clinical safety laboratory abnormalities); treatment-related AEs; severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation; vital sign measurements; and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after each vaccination, and with any Grade 3 or higher solicited AR will be summarized. A 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be summarized. Unsolicited AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

The number of events of solicited ARs, unsolicited AEs/SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be reported in summary tables accordingly. Pregnancy outcomes will also be summarized.

For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the statistical analysis plan (SAP).

Immunogenicity Analyses:

The analyses of immunogenicity will be based on the per-protocol (PP) set. If the number of participants in the full analysis set (FAS) and PP set differs (defined as the difference divided by the total number of participants in the PP set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the immunogenicity endpoints, the geometric mean of specific antibody titers with corresponding 95% CI at each time point and the geometric mean fold rise (GMFR) of specific antibody titers with the corresponding 95% CI at each post-baseline time point over pre-injection baseline at Day 1 will be provided by treatment arm, with adjustment for baseline antibody titer and other potential covariates, including age group and primary vaccine type. Descriptive summary statistics, including median, minimum, and maximum, will also be provided.

For summarizations of geometric mean titer, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

For mRNA-1010, seroconversion rate from baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point. Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination HAI titer ≥ 1:40 or a pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer.

For mRNA-1273, seroresponse is defined as either: participants with GMFR in nAb or (binding antibody) bAb titers of ≥ 4-fold at Day 29 compared to Day 1 in those with baseline titer ≥ LLOQ, or Day 29 titer ≥ 4 × LLOQ if baseline titer is < LLOQ.

The immunogenicity of mRNA-1073 will follow the same rules as mRNA-1010 and mRNA-1273.

Planned Analyses:

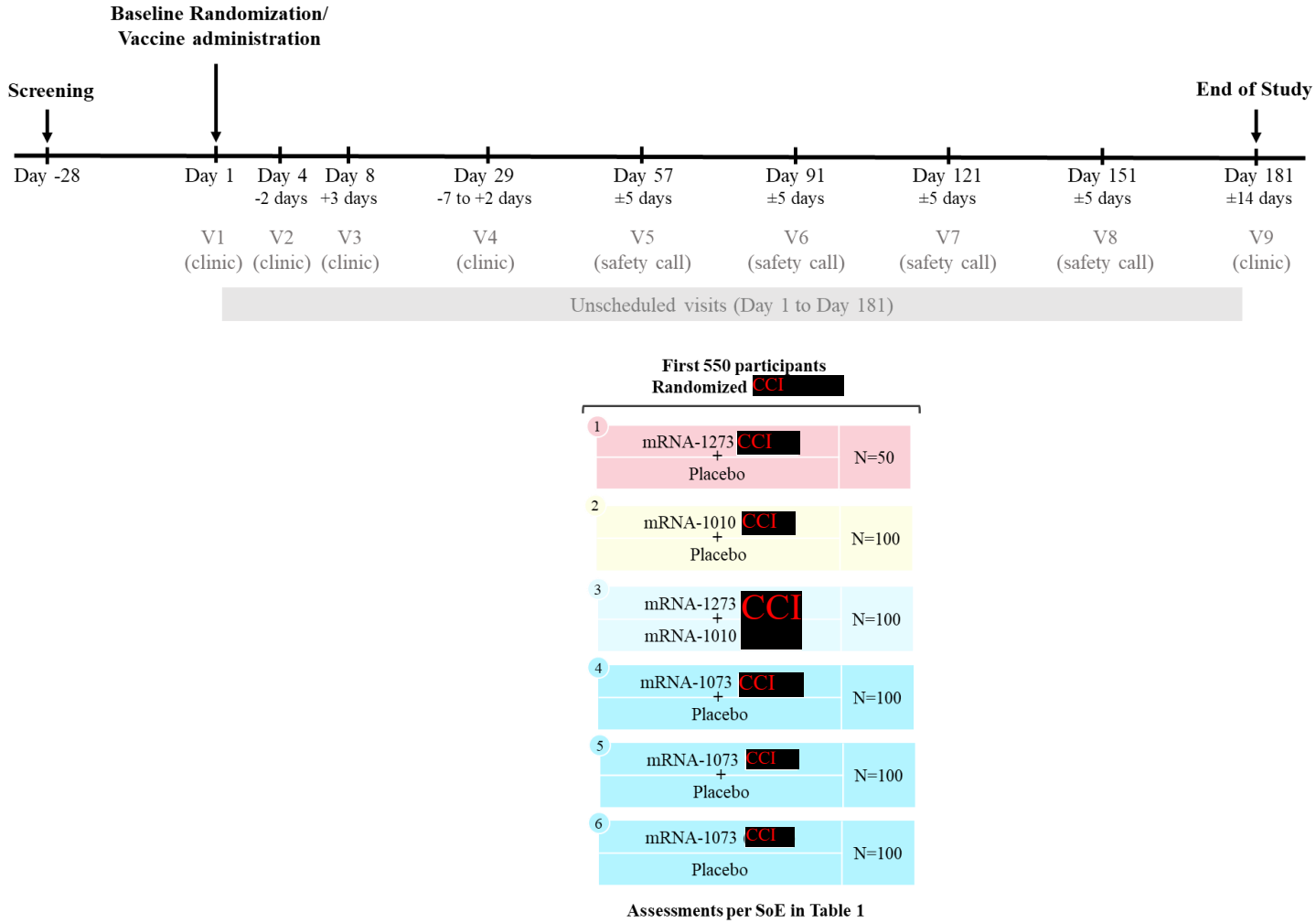
An interim analysis (IA) and a final analysis will be conducted in the study.

The IA will be performed after all the 550 participants randomized into Group 1 through Group 6 have completed their Day 29 visit assessments and will include the safety and immunogenicity data collected up to Day 29. Either nAb or bAb assay will be used for assessment of immunogenicity. The IA will be performed by a separate team of unblinded programmers and statisticians. The analysis will be presented by vaccination groups. Except for a limited number of Sponsor and CRO personnel who will be unblinded to perform the IA, the study site staff, investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis.

The final analysis of all endpoints will be performed after all participants have completed Day 181/EoS. Results of this analysis will be presented in a final clinical study report (CSR), including individual listings. The final CSR will include full analyses of all safety and immunogenicity data through Day 181/EoS. For immunogenicity analysis, either nAb or bAb assays will be used in the study.

1.2. Schema

Figure 1 Study Schema



Abbreviations: SoE = schedule of events; V = visit.

1.3. Schedule of Events

Table 1 Schedule of Events

Visit Number	SCRN	1	2	3	4	5, 6, 7, 8	9	USV
Type of Visit	C	C	C	C	C	SC	C	C
Month Time Point	N/A				M1	M2-M5	M6	Up to M6
Visit Day	Screening[1]	D1 (Baseline)[1]	D4	D8	D29	D57, D91, D121, D151	D181/ EoS	N/A
Window Allowance (Days)	-28	N/A	-2	+3	-7 to +2	±5	±14	N/A
Informed consent form, demographics, concomitant medications, medical history	X							
Inclusion/exclusion criteria	X	X						
Blood collection for safety laboratory samples[2]	X			X				
Full physical examination[3]	X							
Axillary lymph nodes assessment (both arms)[4]		X						
Symptom-directed physical examination[5]		X		X	X		X	X
Vital sign measurements[6]	X	X						
Electrocardiogram (ECG)[7]		X						
Pregnancy testing[8]	X	X						
Randomization		X						
Study vaccination (including 60-minute, post-dose observation period)		X[9]						
Blood collection for humoral immunogenicity[10]		X		X	X		X	
Blood collection for cellular immunogenicity[10]		X		X	X		X	
Optional blood collection for genomics[11]		X						
Optional blood collection for transcriptomics[11]		X		X	X			
Blood sample for potential biomarker analysis[12]			X					
Nasopharyngeal swab for virus detection[13]		X						X
eDiary activation for recording solicited ARs (7 days)[14]		X						

Visit Number	SCRN	1	2	3	4	5, 6, 7, 8	9	USV
Type of Visit	C	C	C	C	C	SC	C	C
Month Time Point	N/A				M1	M2-M5	M6	Up to M6
Visit Day	Screening[1]	D1 (Baseline)[1]	D4	D8	D29	D57, D91, D121, D151	D181/ EoS	N/A
Window Allowance (Days)	-28	N/A	-2	+3	-7 to +2	±5	±14	N/A
Review of solicited AR eDiary				X				
eDiary activation for Symptom Reporting eDiary[15]		X						
Symptom Reporting eDiary for collection of symptoms of ILI and/or COVID-19[16]		Once weekly						
Follow-up safety call[17]						X		
Recording of unsolicited AEs through Day 29		X		X	X			X
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[18]		X		X	X	X	X	X
Recording of non-study vaccinations[18]	X	X		X	X	X	X	X
Study completion							X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; ECG = electrocardiogram; eDiary = electronic diary; EoS = end of study; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (phone) call; SCRN = Screening; USV = unscheduled visit.

1. Screening and Day 1 will NOT be performed on the same day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day Screening window.
2. Safety laboratory tests: Total white blood cell count, hemoglobin, platelets, ALT, AST, creatinine, alkaline phosphatase, and total bilirubin.
3. Physical examination: A full physical examination, including height and weight, will be performed at Screening. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.
4. On the day of vaccination, prior to injection, axillary lymph nodes of both arms should be examined, and any abnormalities should be documented.
5. Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full physical examination will be performed. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.

6. Vital sign measurements: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs will only be collected at Screening and on the day of vaccination (Day 1), once before and at least 60 minutes after vaccination. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.
7. A 12-lead ECG will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to vaccination.
8. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections on Day 1. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The follicle-stimulating hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm menopausal status.
9. All participants will be randomized to receive 2 IM injections, one in each arm, in the deltoid muscle.
10. Samples for humoral immunogenicity and cellular immunogenicity must be collected prior to receipt of vaccination on Day 1. Cellular immunogenicity will be sampled and assessed in a subset of participants.
11. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Blood draws on Day 1 must occur prior to participants being vaccinated.
12. Biomarker plasma and biomarker serum samples will be stored for potential future biomarker assessment.
13. An NP swab specimen for pathogens, including influenza and SARS-CoV-2, will be collected prior to the study injections on Day 1 to document any pre-vaccination infection. An NP swab will also be collected through study completion if any signs or symptoms or an MAAE suggesting influenza, COVID-19, or other causes of upper or lower respiratory infection occur. For signs or symptoms during the study, a participant will be instructed to contact the study site to have an NP swab collected for testing. If the participant cannot or is unable to come into the site to perform the NP swab, every effort should still be made by the site to obtain the NP swab (eg, home visits to collect NP swab for central laboratory testing). Local laboratory testing for influenza and SARS-CoV-2 can be performed in these cases as a backup if NP swab cannot be collected for central laboratory testing.
14. The eDiary entries will be recorded by the participant starting approximately 60 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of vaccination and for 6 days following vaccination. Local solicited ARs will be recorded separately for each injection site. Please see Section 8.4.3 for details.
15. The Symptom Reporting eDiary will be activated for collection of ILI and COVID-19 symptoms.
16. Symptom Reporting eDiary: Participants will be instructed to report via eDiary or telephone calls whether ILI and/or COVID-19 symptoms have been experienced on the following schedule: Once weekly from Day 1 through Day 181/EoS, if symptoms occur, participants will be directed to return to the study site as soon as possible, but no later than 72 hours after the onset of symptoms, for medical evaluation and an NP swab.
17. Trained study personnel will call all participants to collect information related to any SAEs, MAAEs, AESIs, AEs leading to discontinuation, information on concomitant medications associated with those events, and any non-study vaccinations.
18. All concomitant medications and non-study vaccinations will be recorded through 28 days after vaccination; all concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Screening through Day 181/EoS. Historical use of facial injections and dermal fillers for cosmetic or medical indications such as migraine headaches will also be collected.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
bAb	binding antibody
BLA	Biologics License Application
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DSMB	data safety monitoring board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EoS	end of study
EUA	Emergency Use Authorization

Abbreviation or Specialist Term	Definition
EU-CTR	European Union Clinical Trials Regulation
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold rise
GMR	geometric mean ratio
HA	hemagglutinin
HAI	hemagglutination inhibition
HCP	healthcare practitioner
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ILI	influenza-like illness
IM	intramuscular
IND	investigational new drug
IP	investigational product
IRT	interactive response technology
IST	internal safety team
IRB	Institutional Review Board
LLOQ	lower limit of quantification
LTFU	lost to follow-up
MAAE	medically attended adverse event

Abbreviation or Specialist Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
nAb	neutralizing antibody
NH	Northern Hemisphere
NP	nasopharyngeal
PEG-2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PP	per-protocol
PsVNA	pseudovirus neutralization assay
RT-PCR	reverse transcriptase polymerase chain reaction
S-2P	prefusion stabilized Spike protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SH	Southern Hemisphere
SCR	seroconversion rate
SoE	schedule of events
SRR	seroresponse rate
ULOQ	upper limit of quantification
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

2. INTRODUCTION

2.1. Background and Overview

ModernaTX, Inc. (the Sponsor) is developing mRNA-1073, a custom manufactured lipid-encapsulated messenger RNA (mRNA)-based prophylactic vaccine encoding for antigens from influenza viruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). mRNA-1073 encodes for the respective antigens also encoded for by mRNA-1010 and mRNA-1273 (also known as Moderna coronavirus disease 2019 [COVID-19] vaccine).

Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year resulting in a severe challenge to public health (WHO 2018). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the Northern Hemisphere (NH) and Southern Hemisphere (SH) (Riedel et al 2019). Because influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto 2018). Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice per year (once for the NH and once for the SH). Influenza A and influenza B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages).

Currently, licensed seasonal influenza virus vaccines rarely exceed 50% overall effectiveness and are poorly effective during years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2020). Influenza vaccines based on mRNA technology could provide several benefits compared to current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, as well as improved protection in older adults (Rockman et al 2020).

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome. An outbreak of a novel CoV (later designated SARS-CoV-2, the causative agent of COVID-19) initially emerged in Wuhan, Hubei Province, China in December 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020, and COVID-19 continues to have a major global public health impact, with more than 500 million cases and 6.2 million deaths as of 19 Apr 2022 (WHO 2021).

The Sponsor has developed a rapid-response, proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently.

2.1.1. mRNA-1010

The Sponsor is using its mRNA-based platform to develop a custom manufactured lipid nanoparticle-encapsulated, mRNA-based vaccine against diseases caused by influenza virus types A and B. The proposed development candidate mRNA-1010 is a quadrivalent vaccine containing mRNAs that encode for the hemagglutinins (HAs) of the 4 strains recommended by the WHO for cell- or recombinant-based vaccines. Equal amounts of mRNAs that encode for membrane-bound wild-type versions of each of the 4 different strains will be used for the HA components. The mRNA-1010 development candidate will be administered as a single intramuscular (IM) injection and aims to elicit protection from all seasonal influenza viruses covered by the vaccine.

The Sponsor is conducting a first-in-human (FIH) Phase 1/2 study of mRNA-1010 (NCT04956575), a seasonal influenza vaccine, to establish preliminary safety, reactogenicity, and immunogenicity data and recently initiated a pivotal Phase 3 study (NCT05415462) to evaluate the safety and immunological non-inferiority of mRNA-1010 to a licensed seasonal influenza vaccine in adults 18 years and older.

2.1.2. mRNA-1273

mRNA-1273 encodes for the full-length S protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S-2P) in a prefusion conformation. The CoV-S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAbs) that prevent infection (Corbett et al 2020). It has been confirmed that the stabilized SARS-CoV-2 S-2P antigen presents in the correct prefusion conformation (Wrapp et al 2020).

In December 2020, mRNA-1273 was granted Emergency Use Authorization (EUA) in the United States (US) for the prevention of COVID-19 for individuals 18 years of age and older. Additional approvals have been granted for the use of mRNA-1273 globally. mRNA-1273 is currently being evaluated for safety, immunogenicity, and efficacy in ongoing Phase 1 (NCT04283461), Phase 2 (NCT04405076), and Phase 3 (NCT04470427) trials. All 3 trials have been modified to allow for unblinding and crossover or to assess safety and immunogenicity of booster doses of vaccine. In November 2021, the US Food and Drug Administration (FDA)

granted EUA for an mRNA-1273 booster dose (CCI to be given at least 5 months after the primary series with mRNA-1273 in adults aged 18 years and older.

In August 2021, the Sponsor filed a Biologics License Application (BLA) with the FDA for the full licensure of the mRNA-1273 vaccine for active immunization to prevent COVID-19 in individuals 18 years of age and older. In January 2022, the US FDA approved the BLA for SPIKEVAX (mRNA-1273) to prevent COVID-19 in individuals 18 years of age and older.

2.1.3. mRNA-1073

mRNA-1073 is a custom manufactured lipid-encapsulated mRNA-based prophylactic vaccine encoding for antigens from influenza viruses and SARS-CoV-2.

2.2. Study Rationale

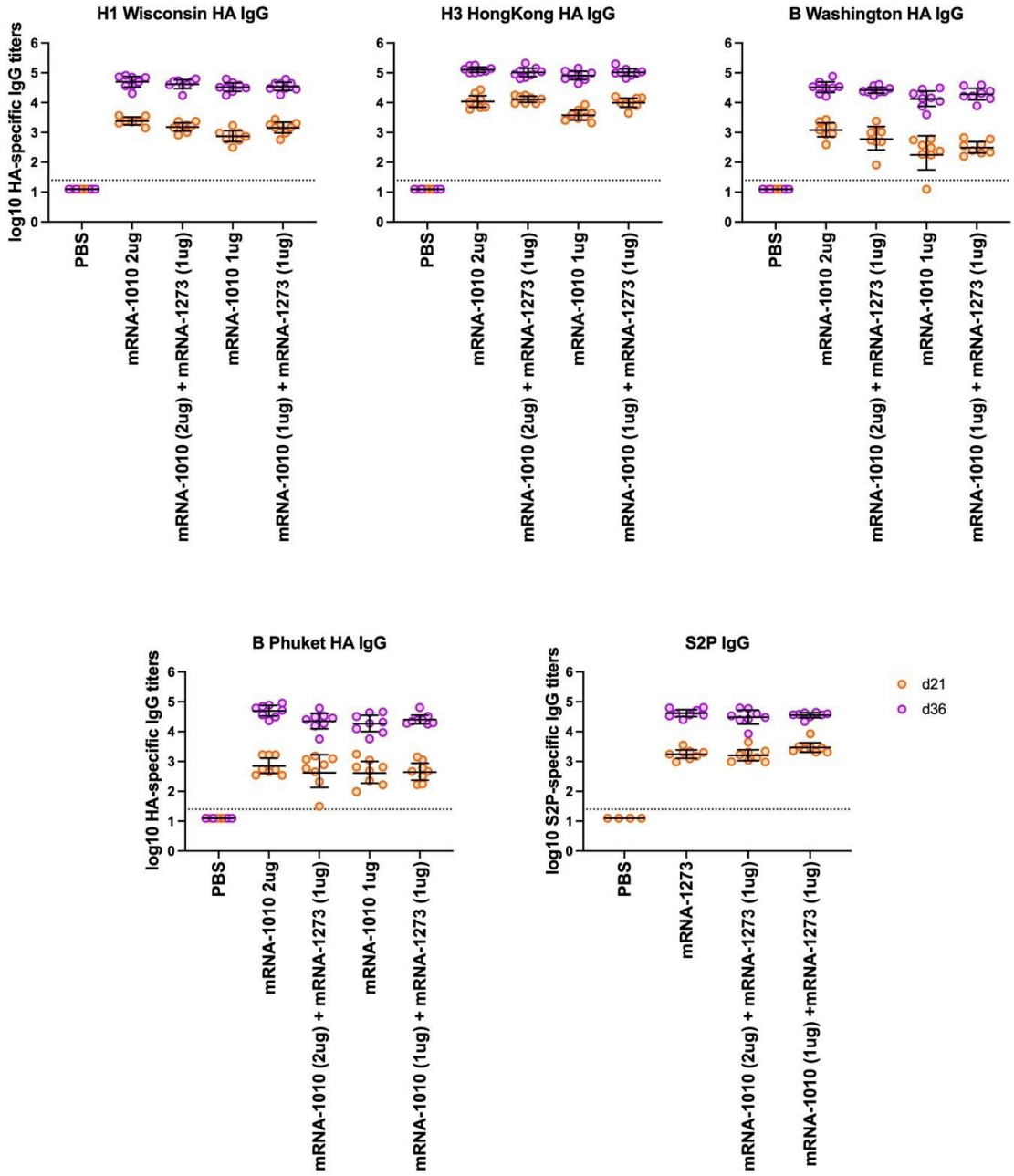
The administration of mRNA-1073 vaccine, encoding for the respective antigens also encoded for by mRNA-1010 (seasonal influenza) and mRNA-1273 (SARS-CoV-2), has the potential to efficiently reduce the overall burden of acute viral respiratory diseases by providing simultaneous protection against influenza and SARS-CoV-2 viruses in a convenient dosing regimen. mRNA-1073 offers greater convenience and has the potential to lead to increased compliance with vaccine recommendations, which has been frequently utilized for pediatric vaccines (Kurosky et al 2017). Furthermore, this combined regimen could provide a public health benefit through synergistically increasing coverage rates against influenza and SARS-CoV-2 viruses. The Sponsor is developing mRNA-1073, a custom manufactured lipid-encapsulated mRNA-based prophylactic vaccine encoding for antigens from influenza viruses and SARS-CoV-2.

This Phase 1/2 study will collect safety and immunogenicity data to further inform the clinical development of mRNA-1073.

2.2.1. Nonclinical Studies

A mouse immunogenicity study has confirmed that a combined vaccination (mixture) with mRNA-1010 and mRNA-1273 results in potent immune responses against all included antigens with no observed immune interference or synergistic or additive responses. Mice were immunized twice with mRNA-1010 or mRNA-1273 or a combination of both (mixed before administration). Antibody titers (immunoglobulin G) were measured against all antigens by enzyme-linked immunosorbent assay (ELISA) post prime (Day 21) and post boost (Day 36), and serological data are depicted in Figure 2.

Figure 2 Mouse Immunogenicity Data



Abbreviations: d21 = Day 21; d36 = Day 36; ELISA = enzyme-linked immunosorbent assay; HA = hemagglutinin; IgG = immunoglobulin G; mRNA = messenger RNA; PBS = phosphate buffered saline; S2P = stabilized SARS-CoV-2 spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

IgG binding antibody titers determined by ELISA using recombinant A/Wisconsin/588/2019 H1, A/Hong Kong/45/2019 H3, B/Washington/02/2019 HA, B/Phuket/3073/2013 HA and SARS-CoV-2 S2P proteins. Titers were determined using a 4-parameter logistic curve fit in GraphPad Prism (GraphPad Software, Inc.) and defined as the reciprocal dilution at approximately OD450nm = 1.5 (normalized to a mouse standard on each plate). Mice were immunized individually with mRNA-1010 (1 µg or 2 µg) or mRNA-1273 (1 µg) or a combination of mRNA-1010 + mRNA-1273 (1 µg + 1 µg [1:1 ratio] or 2 µg + 1 µg [2:1 ratio]). The immunization was a prime/boost regimen with a 3-week interval. d21 = 3 weeks post prime, and d36 = 2 weeks post boost.

Immunogenicity studies in rats (not performed according to Good Laboratory Practice [GLP] standards) with safety endpoints (body weights, clinical observations, hematology, and clinical chemistry) have been completed for the individual vaccines (Seasonal Flu [mRNA-1010, investigational new drug (IND) 27460]; SARS-CoV-2 [mRNA-1273, IND 19635]) used in this study. The studies evaluated the immunogenicity and safety of the vaccine at 30, 60, or 100 µg/dose by IM bolus injection on Days 1 and 22 in Sprague Dawley rats (reports 20287009 and 2308-123, respectively). Both mRNA-1010 and mRNA-1273 were well tolerated at all dose levels and produced robust antibody responses against the target antigen(s). In both studies, there were no test article-related effects on mortality or body weights detected. Clinical observations included transient edema and erythema at the injection site that fully resolved within 4 to 5 days. Hematology and clinical chemistry changes on Day 23 (24 hours post last dose) were generally consistent between the 2 test articles, mild to moderate in magnitude, and indicative of an inflammatory and/or immune response (such as higher neutrophil and eosinophil counts, along with increases in globulin and/or decreases in albumin with a concomitant lower albumin/globulin ratios, compared with control) with or without signs of diminished erythropoiesis (for example, lower reticulocyte counts that lacked corresponding changes in red cell mass parameters) that were considered secondary to the inflammatory/immune response.

Test article related, generally dose dependent clinical pathology changes were observed at ≥ 8.9 µg/dose. Hematology changes included increases in white blood cells, neutrophils, and eosinophils and decreased lymphocytes; coagulation changes included increases in fibrinogen and activated partial thromboplastin time; and clinical chemistry changes included decreases in albumin, increases in globulin, and a corresponding decrease in albumin/globulin ratio. Clinical pathology changes generally reversed or were reversing by the end of the 2-week recovery period. Test article related, transient cytokine increases were observed at ≥ 8.9 µg/dose at 6 hours after dosing, including IP-10, MCP1, and MIP-1-α. Cytokine changes were generally reversing by the end of the 2-week recovery period.

Overall, the findings of mRNA-1010 and mRNA-1273 in these non-GLP, repeat-dose rat studies were consistent with the aggregate GLP platform toxicology package.

2.2.2. Clinical Studies

No clinical studies of combined administration of mRNA-1010 and mRNA-1273 or with mRNA-1073 have been performed to date.

Development of mRNA-1273 is outlined in Section 2.1.2.

The Sponsor is currently evaluating mRNA-1010 in the mRNA-1010-P101 study (NCT04956575), the FIH Phase 1/2 clinical study to establish preliminary safety and immunogenicity data at 3 dose levels of vaccine (50, 100, and 200 µg) against a placebo control.

The study comprises 3 parts with a total of 880 participants: Phase 1/2 (placebo-controlled), Phase 2 NH (active-controlled), and Phase 2 Extension (active-controlled). The Phase 1/2 and Phase 2 NH parts are completed and have evaluated mRNA-1010 at doses of 25, 50, 100, and 200 µg. An additional Phase 2 Extension part is intended to support shelf-life at lower doses (6.25, 12.5, 25 µg), and has been initiated; the Phase 2 Extension will be completed in Q4 2022. In June 2022, the Sponsor began enrolling adult participants ≥ 18 years of age in the mRNA-1010-P301 study, a randomized, observer-blind, Phase 3 safety and immunogenicity of mRNA-1010 (50 µg) vs. an active comparator (Fluarix). The selection of the 50 µg dose level is supported by the data from the Phase 1/2 and the Phase 2 NH interim analyses demonstrating an acceptable safety and reactogenicity profile and robust HAI responses for H1N1 and H3N2 strains with Day 29 geometric mean titers (GMTs) that were higher than the licensed comparator.

There is also precedence for co-administering mRNA-1273 with an influenza vaccine. Interim results from the co-administration study of mRNA-1273 boost (100 µg) and Fluzone High-Dose Quadrivalent vaccines in approximately 300 adults 65 years and older demonstrated similar safety, tolerability, and immunogenicity responses compared to each vaccine administered individually (NCT04969276).

2.3. Benefit/Risk Assessment

2.3.1. Potential Benefits of Study Participation

The following benefits may accrue to participants who receive mRNA-1010 and/or mRNA-1273 vaccine as booster doses:

- The mRNA-1273 vaccine as a booster dose may provide improved protection against SARS-CoV-2 and its variants.
- Participants will have a baseline (Day 1) evaluation for respiratory pathogens, including influenza virus and SARS-CoV-2, and ongoing surveillance for influenza-like illness (ILI) and/or COVID-19 throughout the study.
- The study will contribute to the development of a potentially efficacious vaccine against seasonal influenza virus and SARS-CoV-2 given together as a single injection.

2.3.2. Risks from Study Participation and Their Mitigation

Adverse events (AEs) ranging from immediate mild allergic reactions (eg, urticaria) to systemic allergic reactions (eg, anaphylaxis) may occur following any vaccination. Systemic allergic reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). Since the authorization

of the mRNA-1273 vaccine for COVID-19, the US Centers for Disease Control and Prevention (CDC) estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precaution, all participants will remain under observation at the study site for a minimum of 60 minutes after injection.

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

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the proprietary SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate) lipid formulation have commonly resulted in transient and self-limiting local inflammatory reactions. These typically included pain, erythema (redness), or swelling (hardness) at the injection site, which were mostly mild to moderate in severity and usually occurred within 24 hours of injection. Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection have been observed in early phase clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time.

In an ongoing Phase 3 study of mRNA-1273 vaccine for COVID-19 in 30,346 adults, the most commonly reported local reactions included injection site pain, axillary lymphadenopathy, and injection site erythema. Most of these reactions were Grade 1 or 2 in severity and resolved within 3 to 4 days of onset. The most commonly reported systemic reactions were fatigue, headache, myalgia, arthralgia, and chills. In most cases, the reactions resolved spontaneously within several days.

In the post-authorization setting, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Investigators and study participants should be alert to the signs and symptoms of myocarditis and pericarditis. The risk of myocarditis after a third dose (0.5 mL, CCI) or booster dose (0.25 mL, CCI) of the Sponsor's COVID-19 vaccine has not yet been characterized.

2.3.3. Overall Benefit/Risk Conclusion

Safety and immunogenicity data from the interim analyses of the mRNA-1010-P101 study (Phase 1/2 and Phase 2 NH study portions) demonstrated no significant safety concerns (doses tested ranged from CCI of mRNA-1010). Vaccination with mRNA-1010 elicited

hemagglutination inhibition (HAI) antibodies against all strains at all dose levels in the Phase 1/2 portion (see Section 4.3 and the mRNA-1010 Investigator's Brochure [IB]).

While efficacy has been established for mRNA-1273, the combined administration of mRNA-1010 and mRNA-1273 as separate vaccines or as mRNA-1073 may or may not offer further protection against seasonal influenza and COVID-19, respectively.

Safety findings will be monitored and periodically reviewed by the study team members, an internal safety team (IST), and DSMB to evaluate the safety status of all participants. The IST and DSMB will review and assess the safety data as described in Section 8.5. All participants will be followed up for 6 months after the study vaccination.

Considering the nonclinical data for the combined administration of mRNA-1010 and mRNA-1273 vaccines and the safety and immunogenicity data for mRNA-1010, mRNA-1273, and other mRNA vaccines manufactured to date by the Sponsor that contain the proprietary SM-102 lipid formulation, the Sponsor considers the potential benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are described in Table 2.

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of study vaccines	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period post vaccination • Frequency and severity of any unsolicited AEs during the 28-day follow-up period post vaccination • Frequency of any SAEs, AESIs, MAAEs, and AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
• To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 across study vaccine arms at Day 29	• GMT and GMFR at Day 29 compared with Day 1 (baseline) by HAI assay for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer ≥ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is ≥ 1:10 in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥ 4-fold if baseline is ≥ LLOQ or ≥ 4 × LLOQ if baseline titer is < LLOQ in nAb titers measured by PsVNA (or binding antibody assay)
• To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 at all evaluable humoral immunogenicity time points	• GMT and GMFR compared with Day 1 (baseline) by HAI for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2 • Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) as defined above

Objectives	Endpoints
Exploratory (may be performed)	
• To evaluate the humoral immunogenicity against vaccine mismatched strains	• GMT and GMFR (compared to Day 1) to vaccine mismatched strains
• To evaluate the humoral immunogenicity against vaccine-matched and mismatched strains using alternative methods	• GMT and GMFR (compared to Day 1) to vaccine-matched and mismatched strains assayed by alternative methods (eg, microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2)
• To evaluate cellular immunogenicity in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells and T cells after vaccination
• To further characterize the immune response across study vaccines	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
• To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates	• Frequency of laboratory-confirmed clinical influenza and COVID-19 and assessment of immune responses to infection and viral isolates

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

4. STUDY DESIGN

4.1. General Design

This is a Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 compared to co-administered mRNA-1010 and mRNA-1273 vaccines and to the individual vaccines alone in healthy adults 18 to 75 years of age.

Participants in the study will participate in a Screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and a follow-up period (up to 6 months after vaccination). The study schema is presented in Figure 1.

On Day 1, each participant will receive 2 injections administered IM, one in each arm, in the deltoid muscle. The vaccines to be tested include: 1) mRNA-1273 vaccine encoding for the full-length S protein of SARS-CoV-2, modified to introduce S-2P in a prefusion conformation; 2) mRNA-1010 vaccine encoding for the HA surface glycoproteins of the 4 strains by the WHO for the 2022 SH influenza season cell- or recombinant-based vaccines; and 3) mRNA-1073 vaccine encoding for the respective antigens also encoded for by mRNA-1010 and mRNA-1273. The placebo and the diluent for mRNA-1073 vaccine will be 0.9% sodium chloride (normal commercial saline) injection, which meets the criteria of the US Pharmacopeia (USP).

The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine (primary series or booster) must be ≥ 120 days prior (or less per local guidance) to the randomization visit. Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have no known history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening. Randomization will be stratified by age (18 to 49 years old and 50 to 75 years old, balanced across the 2 age groups within each vaccination group). A complete listing of inclusion and exclusion criteria is provided in Section 5. The numbers of participants and groups are shown in Table 3.

Table 3 Study Arms

#	Group Name	Sample Size (N=550)
1	mRNA-1273 CCI + placebo	50
2	mRNA-1010 + placebo	100
3	mRNA-1010 + mRNA-1273 CCI co-administration	100
4	mRNA-1073 CCI + placebo	100
5	mRNA-1073 placebo	100
6	mRNA-1073 placebo	100

The Schedule of Events (SoE) is provided in Table 1.

Participants will have 6 visits and 4 safety phone calls. Vaccines (mRNA-1073, mRNA-1010, or mRNA-1273) and placebo (as indicated) will be administered as IM injections, one in each arm, in the deltoid muscle. Safety and/or immunogenicity and/or biomarkers study visits will occur on Days 4, 8, 29, and 181 (end of study [EoS]). Study visits will include scheduled safety phone calls at Days 57, 91, 121, and 151 to collect adverse events (AEs), medically attended AEs (MAAEs), AEs of special interest (AESIs), AEs leading to withdrawal, serious adverse events (SAEs), and information about concomitant medications and receipt of non-study vaccinations.

At the dosing visit on Day 1, participants will be instructed how to record solicited ARs within the provided electronic diary (eDiary). Solicited ARs will be collected for 7 days (the day of injection and the following 6 days), and local solicited ARs will be collected separately for each injection site. Unsolicited AEs will be collected for 28 days (the day of injection and the following 27 days) after injection; SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be collected throughout the study. All participants will be tested for the presence of SARS-CoV-2 and influenza antigens at baseline via nasopharyngeal (NP) swabs (Day 1) and at any unscheduled visits. Blood draws will be collected on Days 1, 8, 29, and 181/EoS. There will be an additional visit on Day 4 at which blood will be drawn for future biomarker assessment. Optionally, blood draws for genomic analysis will be collected at Day 1 and for transcriptomic analysis at Days 1, 8, and 29. The collected samples will be processed and analyzed per the Laboratory Manual. Active surveillance for intercurrent or breakthrough SARS-CoV-2 infection will occur throughout the study and reported as AEs (confirmed symptomatic infections will be reported as MAAEs if not SAEs). Participants with signs and symptoms meeting the CDC case definition for COVID-19 (21 February 2021 or most recent; CDC 2021b) will be asked to contact the site and undergo prompt assessment, which will include reverse transcriptase polymerase chain reaction (RT-PCR) testing (of a respiratory sample) to assess symptomatic COVID-19. Participants with any clinical or radiographic evidence of pneumonia will also

undergo RT-PCR testing. Suspected COVID-19 cases will also be tested using a multiplex assay to assess for non-SARS-CoV-2 causes of upper or lower respiratory tract infection. Participants will have blood samples collected at scheduled study site visits during the study for immunogenicity assessments or other medical concerns according to the investigator's judgment.

Participants may experience AEs (including symptoms of COVID-19) that necessitate an unscheduled visit. There may also be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

The IST will conduct ad hoc reviews throughout the study, as requested by the study medical monitor and the study team. An independent, unblinded DSMB will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. Safety data will be reviewed as needed when study stopping or pausing criteria are met, or as otherwise requested by the study team and/or IST as described in the DSMB charter. See Section 8.5 for details on the IST and DSMB constituted in this study.

An interim analysis (IA) will be performed after all 550 participants randomized into Group 1 through Group 6 have completed their Day 29 visit assessments and will include the safety and immunogenicity data collected up to Day 29. The final study analysis will be completed for all participants after Day 181/EoS.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

4.2. Scientific Rationale for Study Design

This study is designed as a randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 compared to co-administered mRNA-1010 and mRNA-1273 and to mRNA-1010 vaccine and mRNA-1273 vaccine administered alone in healthy adults 18 to 75 years of age. The purpose of this Phase 1/2 study (mRNA-1073-P101) is to generate sufficient safety and immunogenicity data to enable the initiation of a Phase 2/3 study.

All participants will provide NP swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza virus and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments. Furthermore, NP swab samples for assessment of infection with respiratory pathogens, including influenza virus and SARS-CoV-2, will be collected anytime from Day 1 through Day 181/EoS if the participants have protocol-defined ILI or symptoms suggestive of COVID-19 or other upper or lower

respiratory infection at the investigator's discretion. Additionally, clinical information may be collected to evaluate the severity of the clinical case.

4.3. Choice of Vaccine Doses

The Sponsor is currently conducting mRNA-1010-P101, the FIH Phase 1/2 study of mRNA-1010 to establish preliminary safety, reactogenicity, and immunogenicity data at 3 dose levels of vaccine (CCI) against a placebo control (NCT04956575). The IA1 of safety data at Day 29 of 180 healthy adults (45 participants per group) in the United States showed no significant safety concerns for the doses tested, with the CCI dose of mRNA-1010 having the most favorable reactogenicity profile. The immunogenicity data at Day 29 showed that mRNA-1010 elicited immune responses as measured by HAI for all 4 strains included in the vaccine, across all dose levels and age groups. Encouragingly, all 3 dose levels elicited similar levels of immune responses. Additional information is available in the IB.

The mRNA-1010-P101 study has enrolled 498 adults in a Phase 2 NH cohort in 4 groups: CCI mRNA-1010 (n=151), CCI mRNA-1010 (n=147), CCI mRNA-1010 (n=147), and Afluria (n=53). The IA2 of safety data through Day 29 demonstrated no significant safety concerns. The frequency and severity of the reports of solicited ARs in the mRNA-1010 groups were acceptable across all dose levels.

IA1 and IA2 data through Day 29 for both the Phase 1/2 and the Phase 2 NH portions demonstrated local and systemic solicited ARs to be mostly mild to moderate in severity, without any Grade 4 ARs. There were no AESIs or AEs leading to study pauses. There were no SAEs or AEs leading to study discontinuation that were assessed as related to the study vaccine. Additional information is available in the IB.

The Sponsor developed mRNA-1273, an mRNA-based vaccine against SARS-CoV-2. Having achieved the primary endpoint in a pivotal Phase 3 study for SARS-CoV-2 infection, mRNA-1273 was granted EUA in December 2020 and BLA in January 2022 for the prevention of COVID-19 for individuals 18 years of age and older (Baden et al 2021). Given the potential for waning immunity, the emergence of highly transmissible SARS-CoV-2 variants, and the ability of some variants to partially escape immunity, the Sponsor assessed the immunogenicity and safety of a CCI booster immunization. The FDA has authorized for emergency use the administration of a single booster dose (CCI) of mRNA-1273 vaccine after completing the primary series of this vaccine in individuals 18 years of age and older. Additionally, the FDA recently amended the EUA to authorize a second booster dose for people 50 years of age and older and for certain immunocompromised individuals. Additional information is available in the IB.

Based on the Sponsor's prior studies as described above, mRNA-1073 at dose levels of CCI [redacted] are being assessed and are anticipated to be immunogenic and well tolerated.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed the last scheduled procedure on Day 181 (ie, 6 months after the study vaccination on Day 1), as shown in the SoE (Table 1).

The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure, as shown in the SoE (Table 1), for the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adults 18 to 75 years of age at the time of consent (Screening Visit).
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2 (inclusive) at the Screening Visit.
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized. A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status (please see Section 11.2 for details).
6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
   - Has a negative pregnancy test at the Screening Visit and on the day of vaccination (Day 1).
   - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
   - Has agreed to continue adequate contraception through 3 months following vaccine administration. Adequate female contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label (Appendix 11.2).
   - Is not currently breastfeeding.
7. Participants must have been fully vaccinated for COVID-19 primary series according to the locally authorized or approved regimen, and their last COVID-19 vaccine (primary series or booster) was ≥ 120 days prior to the randomization visit (or less per local guidance).

5.2. Exclusion Criteria

Participants meeting any of the following criteria at the Screening Visit, unless noted otherwise, will be excluded from the study:

1. Participant is acutely ill or febrile (temperature ≥ 38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
2. Participant has a history of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication ≤ 60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition. Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the investigator.
3. Participant has a reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease.
4. Participant has dermatologic conditions that could affect local solicited adverse reaction (AR) assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Participant has a reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA vaccine(s) or any components of the mRNA vaccines.
6. Participant has a reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. Participant has a diagnosis of malignancy within previous 10 years (excluding nonmelanoma skin cancer).
8. Participant has any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.

9. Participant has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 10 mg/day of prednisone or equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are not exclusionary.
10. Participant has received or plans to receive any vaccine authorized or approved by a local health agency ≤ 28 days prior to study injections (Day 1) or plans to receive a vaccine authorized or approved by a local health agency within 28 days before or after the study injections.
11. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine ≤ 180 days prior to the randomization visit.
12. Participant has tested positive for influenza by local health authority approved testing methods ≤ 180 days prior to the Screening Visit.
13. Participant has had close contact to someone with SARS-CoV-2 infection or COVID-19 as defined by the US CDC in the past 10 days prior to the Screening Visit.
14. Participant has known history of SARS-CoV-2 infection within ≤ 90 days.
15. Participant has received systemic immunoglobulins or blood products ≤ 90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study.
16. Participant has a history of myocarditis, pericarditis, or myopericarditis.
17. Participant has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
18. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
19. Participant is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.
20. Participant has clinical screening laboratory values (total white blood cell count, hemoglobin, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, and total bilirubin) > Grade 1 (DHHS 2007).

5.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. Participants in the study should defer vaccination with an approved COVID-19 vaccine

or seasonal influenza vaccine until after completion of their Day 29 visit, and ideally until Day 181 visit, if such vaccines are available, and they have discussed with the investigators and have chosen to receive it.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria, and information on any SAE that may have occurred from the time informed consent was obtained to the time of withdrawal.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time within the 28-day Screening window if they will be eligible upon rescreening.

6. STUDY TREATMENT

6.1. Investigational Products Administered

The term investigational product (IP) refers to mRNA-1073, mRNA-1010, or mRNA-1273 vaccine administered in this study.

mRNA-1073

mRNA-1073 is administered as a single dose and aims to elicit protection from influenza and SARS-CoV-2. mRNA-1073 contains mRNA coding for 4 HA antigens of the influenza virus strains recommended for the 2022 SH seasonal vaccines by the WHO and the mRNA for the S protein of SARS-CoV-2 virus formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG-2000-DMG). mRNA-1073 is based on the antigens encoded for by mRNA-1010 and mRNA-1273 and is intended as a single annual dose for protection from seasonal influenza and SARS-CoV-2. Commercially available 0.9% sodium chloride, USP will be used as appropriate for dose preparation.

mRNA-1010

mRNA-1010 is administered as a single dose and aims to elicit protection from influenza A and B viruses. mRNA-1010 is a quadrivalent vaccine containing mRNAs encoding for the HAs of the 4 strains recommended by the WHO for 2022 SH cell- or recombinant-based vaccines formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG-2000-DMG. Equal amounts of mRNAs encoding for each of the 4 different strains are used for the HA components. mRNA-1010 is administered as a single dose and aims to elicit protection from all seasonal influenza viruses covered by the vaccine.

mRNA-1273

mRNA-1273 is administered as a single dose and aims to elicit protection from SARS-CoV-2. mRNA-1273 contains mRNA CX-024414 encoding for the S-2P of Wuhan-Hu-1. mRNA-1273 consists of the mRNA formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG-2000-DMG.

6.2. Randomization and Blinding

The Sponsor's Biostatistics Department or designee will generate the randomized allocation schedule(s) for vaccination group assignment. Participants will be randomized in a CCI to receive mRNA-1273 (CCI + placebo (50 participants), mRNA-1010 CCI + placebo (100 participants), mRNA-1010 (CCI + mRNA-1273 CCI co-administration

(100 participants), mRNA-1073 (CCI) + placebo (100 participants), mRNA-1073 (CCI) + placebo (100 participants), or mRNA-1073 (CCI) + placebo (100 participants). Randomization will be stratified by age (18 to 49 years old and 50 to 75 years old, balanced across the 2 age groups within each vaccination group).

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Preparation of Study Vaccine

The IP (mRNA-1073, mRNA-1010, and mRNA-1273) and placebo preparation instructions are detailed in the Pharmacy Manual.

6.3.2. Study Vaccine Administration

mRNA-1073, mRNA-1010, or mRNA-1273 and placebo (if indicated) will be administered as IM injections, one in each deltoid muscle on Day 1, according to the procedures specified in the Pharmacy Manual. Each arm (left and right) and the corresponding vaccine or placebo administered will be recorded by the unblinded site staff and will be kept confidential from other study documents/personnel before unblinding is authorized.

On Day 1, participants will be monitored for a minimum of 60 minutes after vaccination. Assessments will include vital sign measurements and monitoring for local or systemic ARs as shown in the SoE (Table 1).

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

Please see details provided in the Pharmacy Manual.

6.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP (mRNA-1073, mRNA-1010, and mRNA-1273) and placebo (0.9% sodium chloride)
- Confirming the appropriate labeling of the IP, so it complies with the legal requirements of the United States

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the site, which includes the following:

- Confirming that the IP was received in good condition

- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of IP are described in the Pharmacy Manual.

6.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of the IP. Sterile mRNA-1073, mRNA-1010, and mRNA-1273 are packaged in 2R glass vials. The IP will have all required labeling per regulations.

The IP will be packaged and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, Code of Federal Regulations (CFR) Title 21 Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.3.5. Study Vaccine Storage

mRNA-1073 and mRNA-1010 must be stored at -25°C to -15°C (-13°F to 5°F) in a secure area with limited access and must be protected from moisture and light until they are prepared for administration (Section 6.3.1). mRNA-1273 must be stored at -90°C to -60°C in a secure area with limited access and must be protected from moisture and light until it is prepared for administration (Section 6.3.1). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. It is recommended that there should be an available backup freezer. It is also recommended that the freezer should be connected to a backup generator. In addition, for IP accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IP that was not temperature controlled during shipment or storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods. The 0.9% sodium chloride injection (USP) should be stored at 20°C to 25°C (68°F to 77°F) in a restricted access area.

6.3.6. Study Vaccine Accountability

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

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

6.3.7. Study Vaccine Handling and Disposal

A site monitor will reconcile the IP inventory during the conduct and at the EoS for compliance. Once reconciled at the site at the EoS, the IP should be destroyed on site, if site procedures allow, or returned to a destruction depot per instruction of the Sponsor. Additional details are found in the Pharmacy Manual.

6.4. Study Intervention Compliance

All IPs will be administered at the study site under direct observation of medically qualified unblinded study staff and appropriately recorded (date and time) in the eCRF. The qualified unblinded staff will confirm that the participant has received the entire dose of IP and will record the injection site (left or right deltoid) and the corresponding vaccine or placebo administered and will keep the information confidential from other study documents/personnel until unblinding is authorized. If a participant does not receive IP or does not receive all of the planned dose, the reason for the missed dose will be recorded. Data will be reconciled with site accountability records to assess compliance.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window specified in the SoE (Table 1). If a participant does not complete a visit within the time window, that visit may be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

6.5. Prior and Concomitant Medications

6.5.1. Prior Medications and Therapies

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

6.5.2. Concomitant Medications and Therapies

At study site, study staff must question the participant regarding any medications taken and non-study vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the study injection and through Day 181/EoS.
- Any seasonal influenza vaccine administered since April 2021.
- Any authorized or investigational COVID-19 vaccine at any time before the IP injection.
- All concomitant medications taken through 28 days after vaccination. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Systemic steroids (≥ 10 mg/day of prednisone or equivalent), immunosuppressants, immune-modifying drugs, immunoglobulins, and/or blood products administered at any time during the study period after the IP injection.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or an MAAE from Day 1 through Day 181/EoS.
- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after vaccination, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the post-injection study visits or via other participant interactions (eg, telephone calls).
- Historical use of facial injections or dermal fillers, for cosmetic or medical indications such as migraine headaches.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Global.

If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

6.5.3. Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant From Per-Protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IPs used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 10 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- An authorized or licensed vaccine administered during the period from 28 days before through 28 days after vaccination.
- Immunoglobulins and/or any blood products administered during the study period.
- Antiviral and antiretroviral medications.

6.6. Intervention After the End of the Study

Investigational product will not be available to the participants following the end of the study.

7. DELAY OR DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Pause Rules

Study pause rules will be continuously monitored during all periods of the study by the investigators, IST, and DSMB (as warranted). If the investigator, IST, or DSMB request that the study be paused due to a safety concern, further study vaccination will be suspended, but all other planned procedures relating to safety, reactogenicity, and immunogenicity assessments will continue as described in the study protocol. An unblinded statistician will support the determination if study pause rules have been met. The IST will be composed of the Sponsor's physicians. The Sponsor will notify the Center for Biologics Evaluation and Research within 48 hours in the event of a study pause.

7.1.1. Pause Rules Based on the Occurrence of a Single Event and Adjudicated by the Data and Safety Monitoring Board

The occurrence of any of the events listed in Table 4, regardless of vaccination group, will result in immediate suspension of dosing and enrollment. An unscheduled DSMB will be convened to assess specific data concerns and to make recommendations.

Table 4 Pause Rule Criteria, Events, and Thresholds – Single Event

Pause Rule	Event	Number of Participants
1	Any SAE that cannot be reasonably attributed to a cause other than study vaccination	≥ 1
2	Any Grade 4 AE[1] that cannot be reasonably attributed to a cause other than study vaccination	≥ 1
3	A systemic immediate hypersensitivity reaction within 60 minutes after the study vaccination[2]	≥ 1
4	Suspected or confirmed myocarditis and/or pericarditis	≥ 1

Abbreviations: AE = adverse event; AR = adverse reaction; FDA = Food and Drug Administration; SAE = serious adverse event; US = United States.

[1] Grade 4 AE includes any Grade 4 solicited local or systemic AR and any Grade 4 laboratory abnormality. Grading of laboratory parameters will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007).

[2] Systemic immediate hypersensitivity reaction refers to anaphylaxis as defined in Section 8.4.7.1.

7.1.2. Pause Rules Based on the Occurrence of Events in a Proportion of Participants

The occurrence of safety events that will pause study dosing based on defined threshold levels, which are aggregate incidences relative to the number of exposed participants within a vaccination group, are summarized in Table 5.

Table 5 Pause Rule Criteria, Events, and Thresholds – Proportion of Participants

Pause Rule	Event	Number or Percentage of Participants[1]
5	Any Grade 3 solicited local AR lasting more than 48 hours, within the 7-day, post-vaccination period	≥ 2[2] participants per group or ≥ 20% of participants
6	Any Grade 3 solicited systemic AR lasting more than 48 hours (24 hours for fever) that cannot be reasonably attributed to a cause other than vaccination, within the 7-day, post-vaccination period	≥ 2[2] participants per group or ≥ 20% of participants
7	Any severe unsolicited AE in a vaccination group that cannot be reasonably attributed to a cause other than vaccination OR Any Grade 3 laboratory abnormality[3] in a vaccination group that cannot be reasonably attributed to a cause other than vaccination	≥ 2[2] participants per group or ≥ 20% of participants

Abbreviations: AE = adverse event; AR = adverse reaction; FDA = Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory Activities; US = United States.

[1] The rate of AEs and laboratory abnormalities will be computed based on the number of exposed participants who have provided safety data (ie, have completed a postdosing visit for assessment of safety).

[2] For the first 9 participants in each vaccination group, the pause rule will be considered to be met if 2 of the first 9 participants experience the same solicited AR or the same MedDRA preferred term unsolicited AE or laboratory abnormality. The calculation for ≥ 20% of participants in the expansion stage includes exposed participants in the initial stage and the expansion stage as the total number of participants in the denominator.

[3] Grading of laboratory parameters (specified in Section 8.1.5) will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007).

If a pause is triggered in the study, each participant's study site visits will continue until EoS. If a pause affects a participant's Vaccination Visit, the window for that participant's Vaccination Visit will be suspended until the pause is lifted and vaccination can resume. Once the pause is lifted, vaccination should be reinstated as soon as possible.

If a participant is in the Screening period for more than 28 days as the result of a pause, the participant may be rescreened for study eligibility (and will receive a new screening number) as long as the participant continues to provide consent to participate in the study.

7.2. Criteria for Delay of Vaccine Administration

7.2.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature must be measured before vaccination. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may be injected at a later date within the time window specified in the SoE (Table 1), or the participant may be discontinued from dosing at the discretion of the investigator (Section 7.3):

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

Participants with a fever ≥ 38.0°C (100.4°F) will be contacted within the time window acceptable for participation and reevaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

The investigator, in consultation with the Sponsor's medical monitor, may withhold the IP injection if the participant meets any of the following criteria:

1. Becomes pregnant.
2. Develops symptoms or conditions listed in the exclusion criteria.
3. Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the investigator, requires withholding of vaccine.

The reason(s) for withholding the injection will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 6.5.3).

7.3. Participant Discontinuation/Withdrawal From the Study

Participants who withdraw or are withdrawn from the study will not be replaced.

A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

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

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

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

- AE (specify)
- AESI (specify)
- SAE (specify)
- Solicited AR or reactogenicity event (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

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

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

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 11.1.6).

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All

biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

7.4. Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- If the registered/certified letter is signed by the subject but no other contact is established, the subject is considered to be noncompliant with study visits or procedures and will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 11.1.6). Participants will undergo study procedures at the time points specified in the SoE (Table 1). A participant can also be seen for an unscheduled visit at any time during the study. Reasons for an unscheduled visit may include, but are not limited to, reactogenicity issues, symptoms of potential ILI and/or COVID-19, or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency," investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoE (Table 1). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the study.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The Screening Visit and Day 1 visit will not be performed on the same day. Additionally, the Screening Visit assessments may be performed over multiple visits if within the 28-day Screening window.

8.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoE (Table 1):

- Solicited local and systemic ARs (Section 8.4.3) that occur during the 7 days following vaccine administration (ie, the day of study injections [Day 1] and 6 subsequent days).

Solicited ARs will be recorded daily using electronic diaries (Section 8.1.1). Local solicited ARs will be recorded separately for each injection site.

- Unsolicited AEs observed or reported during the 28 days following vaccination (ie, the day of injection [Day 1] and 27 subsequent days). Unsolicited AEs are defined in Section 8.4.1.
- SAEs, AESIs, MAAEs, and AEs leading to discontinuation from study participation from vaccination on Day 1 through Day 181/EoS or withdrawal from the study.
- Results of safety laboratory tests (Section 8.1.5).
- Vital sign measurements (Section 8.1.4).
- Physical examination findings (Section 8.1.6).
- Symptom Reporting eDiary for ILI and COVID-19 from Day 1 through Day 181/EoS as described below in Section 8.1.8.
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study (Section 8.4.8).

The incidence and severity of the above events will be monitored by an IST as per the charter.

8.1.1. Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary (for 7-day reactogenicity). The local and system ARs that will be solicited by the eDiary are described in Table 6. Participants will also use the Symptom Reporting eDiary to record any ILI and/or COVID-19 symptoms that they experience after vaccination from Day 1 through Day 181/EoS.

On Day 1 (dosing day), participants will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

On Day 1 (dosing day), participants will record data into the eDiary starting approximately 60 minutes after the injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 8.4.3.

- For symptom reporting for ILI and SARS-CoV-2 (Section 8.4.5 and Section 8.4.6), participants will be instructed to report whether these symptoms have been experienced, once weekly from Day 1 through Day 181/EoS, via eDiary or telephone calls. If there is no response to an eDiary prompt for 2 consecutive entries, the study site staff will contact the participant by telephone. The results of the safety call should be recorded in the appropriate source documentation.
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Other measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler provided by the study site.
- Record whether any medications were taken to treat or prevent pain or fever on Day 1 or for the next 6 days.

Study site staff will review eDiary data with participants during the Day 8 visit (Visit 3) after vaccination.

8.1.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants to assess body temperature and injection site reactions, respectively, for recording solicited ARs in the eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

8.1.2. Safety Telephone Call

A safety telephone call is a telephone call made to the participant by a trained site personnel. This call will follow a Sponsor-approved script, which will facilitate the collection of relevant safety information. Safety calls by the site to each participant will occur at the time points indicated in the SoE (Table 1). The participant will be interviewed according to the script about the occurrence of AEs, MAAEs, AESIs, SAEs, AEs leading to discontinuation, concomitant medications associated with those events, and any non-study vaccinations (Section 8.4.9). In addition, study personnel will collect information on known participant exposure to someone with COVID-19 or SARS-CoV-2 infection and on the participant's experience of COVID-19 symptoms. All safety information collected from the telephone call must be documented in the source documents as described by the participant and not documented on the script used for the safety telephone contact. As noted in Section 8.1.1, an unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

8.1.3. Pregnancy Testing

Pregnancy testing includes the following:

- A point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections on Day 1. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.
- If not documented in a female participant's medical records, FSH test may be performed at the Screening Visit, as necessary and at the discretion of the investigator, to confirm menopausal status (please see Section 11.2 for details).

8.1.4. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the SoE (Table 1). On the day of IP administration, vital sign measurements will be collected once before and at least 60 minutes after vaccination. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented in the AE section of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, or is considered stable or until the investigator determines that follow-up is no longer medically necessary.

Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 may be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses may be vaccinated at the discretion of the investigator.

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

8.1.5. Safety Laboratory Assessments

Blood samples for safety testing will be taken at Screening and Day 8. Safety laboratory tests will include total white blood cell count, hemoglobin, platelets, ALT, AST, total bilirubin, alkaline phosphatase, and creatinine. Any clinically significant finding (DHHS 2007) identified on the safety laboratory testing should be reported as an AE.

Additional blood samples for safety laboratory tests may be taken at the discretion of the investigator if warranted to ensure participant's safety.

8.1.6. Physical Examinations

A full physical examination, including height and weight, will be performed at the Screening Visit as indicated in the SoE (Table 1). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. At Screening, the BMI will be calculated using the formula weight (kg) / (height [m])^2. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On the day of vaccination, prior to injection, both arms and associated lymph nodes should be examined, and any abnormalities should be documented.

8.1.7. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to vaccination. Skin preparation should be thorough and electrode placement should be according to standard 12-lead ECG procedure. The purpose of the ECG is to serve as a baseline comparison, should it be necessary, for subsequent clinical evaluation of suspected myocarditis/pericarditis. The ECG output should be filed in the participant's binder. No additional action (including review/interpretation) is required.

8.1.8. Assessment for Respiratory Viral Infection

During the study, participants might experience symptoms consistent with ILI or SARS-CoV-2 infection.

All participants will provide NP swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments (CDC 2021b).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect an NP swab (Table 1) to test for presence of respiratory pathogens (including influenza viruses and SARS-CoV-2) via RT-PCR if a participant experiences:

- Symptoms of ILI or SARS-CoV-2 infection (for definitions, see Section 8.4.5 and Section 8.4.6).

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case. All findings will be recorded in the eCRF.

- Participants will be instructed to report via Symptom Reporting eDiary or telephone calls whether ILI/COVID-19 symptoms have been experienced (see Section 8.4.5 and Section 8.4.6 for symptoms), once weekly from Day 1 through Day 181/EoS. If symptoms occur, participants will be directed to return to the study site as soon as possible, but no later than 72 hours after the onset of symptoms, for medical evaluation and an NP swab. Participants will be contacted by the study site if they have missed reporting in the eDiary. If there is no response to an eDiary prompt for 2 consecutive entries, the study site staff will contact the study participant by telephone.

It is important to note that some of the symptoms of ILI and COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1073, mRNA-1010, and mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgment to decide whether an NP swab should be collected. The collection of an NP swab prior to the Day 1 vaccination can help ensure that cases of influenza or COVID-19 are not overlooked. Any study participant reporting symptoms consistent with protocol-defined ILI (Section 8.4.5) or COVID-19 (Section 8.4.6) during the 7-day period after vaccination should be evaluated for COVID-19 and influenza.

If scheduled, a study site illness visit may include additional assessments such as medical history and physical examination. The NP swab sample may be tested by multiplex RT-PCR for respiratory viruses besides SARS-CoV-2 and influenza to evaluate the severity of the clinical case.

All cases that meet the CDC definition of ILI and/or COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome.

8.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE (Table 1). Immunogenicity assessments will be performed for all participants. Immune response to influenza vaccine antigens will be using HAI assay, with potential utilization on microneutralization assay for influenza strains that do not perform favorably in the HAI assay. Immune responses to SARS-CoV-2 vaccine antigens will utilize either pseudovirus neutralization (PsVNA) nAb assay or multiplex bAb assay, depending on the timing of data delivery. The following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay

- Influenza: Serum nAb level as measured by microneutralization assay as potential substitution to the HAI assay
- SARS-CoV-2: Serum nAb titers as measured by PsVNA and potentially serum binding antibody titers by ELISA or multiplex assay specific to the SARS-CoV-2 proteins
- Cellular immunogenicity in a subset of participants

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual date and time of each sample will be collected. Unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Measurement of antibody levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 11.1.6), excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to influenza and SARS-CoV-2 viruses, additional assay development, and the immune response across influenza viruses.

8.3. Efficacy Assessments

While the study will not be powered for efficacy assessments, symptoms of infection with respiratory pathogens will be tracked as an exploratory objective in this study.

8.4. Safety Definitions and Related Procedures

8.4.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug/vaccine in humans, whether or not considered related to the drug/vaccine.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition, after the IP injection.
- New conditions detected or diagnosed after the IP injection even though they may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

- Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure).

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 8.4.3). For the purposes of IND safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, 7 days after vaccination).

An incidental, asymptomatic RT-PCR confirmed COVID-19 case (ie, workplace screening) should be reported as an unsolicited AE of "asymptomatic COVID-19" if occurring during the first 28 days post study vaccination unless the RT-PCR test was performed on the NP swab collected prior to study vaccination (Day 1).

8.4.2. Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the IP.
- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as AEs; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be

recorded as a separate SAE. Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure) are not considered SAEs.

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4.3. Solicited Adverse Reactions

The term “reactogenicity” refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.1.1). Participants will record such occurrences in an eDiary during the 7 days after vaccination (ie, the day of injection [Day 1] and 6 subsequent days). Local solicited ARs will be recorded separately for each injection site.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 6 modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a participant reported a solicited AR during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity page of the eCRF. If the event starts during the solicited period, but continues beyond 7 days after dosing, the site should collect an end date from the participant to close out the event on the Reactogenicity page of the eCRF. If the participant reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF.

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

Table 6 Solicited Adverse Reactions and Grades

Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Headache	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

Abbreviations: AE = adverse event; eCRF = electronic case report form.
Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the Investigator.
Source: Modified from DHHS 2007.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff on the reactogenicity page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP), to be recorded as an MAAE (Section 8.4.4).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days post injection.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

8.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP, including telephone calls. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory follow-up, COVID-19 [Section 8.1.8]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured on the AE page of the eCRF.

All cases of RT-PCR-confirmed ILI and/or confirmed COVID-19 will be recorded as MAAEs.

8.4.5. Influenza-like Illness

A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom or the occurrence of any 2 or more respiratory symptoms.

Respiratory Symptoms	Systemic Symptoms
1. Sore throat 2. Cough/rhinorrhea/nasal congestion (≥ 1 of the 3 symptoms count as 1 respiratory symptom) 3. Sputum production 4. Wheezing 5. Difficulty breathing	1. Body temperature > 37.2°C (> 99°F) 2. Chills 3. Tiredness 4. Headache 5. Myalgia 6. Nausea/Vomiting 7. Diarrhea

A CDC-defined ILI is defined as body temperature ≥ 37.8°C (100°F) accompanied by a cough and/or sore throat.

An RT-PCR-confirmed influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR done within 7 days of onset of protocol-defined ILI at any setting during the study period.

8.4.6. Suspicion of SARS-CoV-2 Infection

SARS-CoV-2 should be suspected if the participant experiences the acute onset or worsening of any one of the symptoms listed below (CDC 2021c):

- Fever (temperature ≥ 38.0°C [100.4°F]) or chills (of any duration)
- Cough (of any duration)
- Shortness of breath and/or difficulty breathing (of any duration)
- Nausea, vomiting or diarrhea (of any duration)
- Fatigue (lasting ≥ 48 hours)
- Muscle or body aches (lasting ≥ 48 hours)
- Headache (lasting ≥ 48 hours)
- New loss of taste and/or smell (lasting ≥ 48 hours)
- Sore throat, congestion, or runny nose (lasting ≥ 48 hours)

Symptomatic COVID-19 is defined by the presence of one of the above CDC-listed symptoms (CDC 2021c) and a positive RT-PCR test on a respiratory sample. Asymptomatic SARS-CoV-2

infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test result at the time of enrollment, with the serologic assay detecting previously resolved SARS-CoV-2 infections that may have occurred between visits, and the RT-PCR to detect active viral infection at the time of a visit. If participants are confirmed to have SARS-CoV-2 infection and are symptomatic or asymptomatic, the investigator will notify the participants' primary care physicians of the diagnosis and the local public health authorities as required per local regulations.

8.4.7. Adverse Event of Special Interest

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

Section 11.3 (Appendix 3) provides a list of AESIs pertinent to this study.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the electronic data capture (EDC) system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox, or the SAE Fax line (Section 8.4.13).

8.4.7.1. Anaphylaxis

All suspected cases of anaphylaxis should be recorded as MAAEs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours per Section 8.4.13. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as described below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

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

Anaphylaxis is a clinical syndrome characterized by the following:

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

8.4.7.2. Myocarditis/Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (Section 8.4.2). The CDC case definition is provided in Section 11.4 (Appendix 4) as guidance.

8.4.8. Recording and Follow-up of Pregnancy

Female participants who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test at any time during the study should receive no further dosing with IP but should remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study. If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered as SAEs.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence, using the paper Pregnancy Reporting Form provided by the Sponsor. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal

and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

8.4.9. Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected from Day 1 through 7 days after vaccination. Other (unsolicited) AEs will be collected from Day 1 through 28 days after vaccination.

The MAAEs, AESIs, AE leading to withdrawal, and SAEs will be collected from participants as specified in the SoE (Table 1) until the end of their participation in the study. Any AEs occurring before receipt of IP will be analyzed separately from AEs occurring after receipt of the study vaccine(s).

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including respiratory viral infection and COVID-19 symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, physical examination findings, or data relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.4). All contacts, or contact attempts, concerning follow-up of AEs/SAEs should be recorded in the participant's source documentation.

8.4.10. Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.4.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and

systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.4.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- **Mild**: These events do not interfere with the participant's daily activities.
- **Moderate**: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- **Severe**: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.4.11. Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- **Not related:** There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.
- **Related:** There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

8.4.12. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time of screening but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

8.4.13. Reporting Serious Adverse Events

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

Any AE that meets SAE criteria (Section 8.4.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The investigator will assess whether there is a reasonable possibility that the IP caused the SAE as described in Section 8.4.11.

If the eCRF is unavailable at the time of the SAE, the paper SAE/AESI reporting form provided by the Sponsor is to be used for SAE reporting.

The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly. Regulatory reporting requirements for SAEs are described in Section 8.4.18.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to IP or study procedures, or caused the participant to discontinue the study until they are considered resolved or clinically stable, per the investigator's judgement.

8.4.14. Reporting of Adverse Events of Special Interest

The following process for reporting an AESI ensures compliance with 21 CFR 312 and ICH GCP guidelines. After learning that a participant has experienced an AESI, the investigator or

designee is responsible for reporting the AESI to the Sponsor, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. If the AESI meets the criteria for an SAE, the SAE reporting procedure should be followed.

8.4.15. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Medical occurrences that begin before IP dosing but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time after IP administration, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant.
- Receiving an unsolicited complaint from the participant.
- Questioning the participant in an unbiased and nonleading manner.

Solicited ARs will be collected from the day of injection through 6 days after vaccination. Other (unsolicited) AEs will be collected from the day of injection through 28 days after vaccination.

Serious AEs (including AESIs) will be collected from the start of IP dosing until the last day of study participation.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on the paper SAE/AESI report form provided by the Sponsor.

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to study drug discontinuation or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after EoS participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

Participants who develop ILI will be followed through 30 days from the onset of ILI, even if Day 30 is beyond Day 181/EoS.

8.4.16. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of study arm or suspected causal relationship to IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

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

8.4.17. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 7.4.

8.4.18. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.5. Safety Monitoring Committees

8.5.1. Internal Safety Team

An internal safety team, inclusive of, at a minimum, the Sponsor's medical monitor, Sponsor's safety physician, and a CRO medical monitor, will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the DSMB. The IST will conduct a scheduled review of safety data after at least 55 participants (approximately 5 participants in Group 1 and approximately 10 participants in Groups 2 to 6) (see Table 3) have completed the Day 8 visit. Enrollment will be ongoing while this review is conducted if no pause rules (Section 7.1) have been met and the study team has not identified any safety concerns. The IST will also conduct ad hoc reviews as requested by the study medical monitor and the study team.

8.5.2. Data and Safety Monitoring Board

The DSMB, composed of external/independent subject matter experts, will conduct both, a scheduled unblinded review of safety data and as needed reviews of safety data if any pause rule is met or as otherwise requested by the study team and/or IST as described in the DSMB charter.

8.5.3. Cardiac Event Adjudication Committee

An independent Cardiac Event Adjudication Committee (CEAC) that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

8.6. Treatment of Overdose

As the study treatment is to be administered by an HCP, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 11.1.8).

8.7. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9. Biomarkers

Immunogenicity assessments are described in Section 8.2. Samples for potential biomarker analysis will be collected from all participants. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Exploratory assessments may include assessment of biomarkers for safety, reactogenicity, and inflammation. Serologic markers of disease severity, immune response to SARS-CoV-2 or influenza, RT-PCR of NP swab or saliva samples, genetic sequences of SARS-CoV-2 or influenza strains isolated from participants' samples, and genomic and transcriptomic samples may also be evaluated.

8.10. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL ANALYSIS PLAN

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

9.1. Blinding and Responsibility for Analyses

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with the following exceptions:

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the IP for all participants. These personnel will have no study functions other than IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded medically qualified study site personnel will administer the IP. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned IA (Section 9.6). Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results to the blinded investigators, study site staff, clinical monitors, or participants.
- The DSMB will review unblinded safety data provided by the independent unblinded statistician to safeguard the interests of clinical study participants and to help ensure the integrity of the study. The DSMB will review unblinded statistical outputs for ad hoc safety reviews triggered by pause rules, should this occur. Section 11.1.11 provides additional information on DSMB and safety review.

The treatment assignment, including the injection site and the corresponding vaccine or placebo administered, will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA will look different from those of placebo. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

9.1.1. Breaking the Blind

Except in the case of medical necessity, a participant's vaccine assignment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the vaccine assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual vaccine assignment, the investigator will make every attempt to contact the CRO's medical monitor, preferably via electronic protocol inquiry platform, to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within interactive response technology (IRT). All unblinding instances will be tracked via an audit trail in IRT and documented in the final study report.

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time point(s) for analysis as outlined in Section 9.1.

9.2. Statistical Hypotheses

No formal hypotheses will be tested. All analyses will be descriptive and presented by vaccine group.

9.3. Sample Size Determination

The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different study groups.

The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine must be ≥ 120 days prior to the randomization visit (or less per local guidance). Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have not had known history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening. The number of participants and groups are shown in Table 3.

Approximately 550 participants will be enrolled at a CCI [redacted] A sample size of 100 participants in one group has at least an 85% (or 95%) probability to observe at least 1 participant with an AE at a true 2% (or 3%) AE rate (Table 7).

Table 7 Randomized Sample Size Calculations

Sample Size	True AE Rate	Probability to Observe 0 AEs	Power to Detect at Least 1 AE
50	0.05	7.7%	92.3%
50	0.03	21.8%	78.2%
100	0.03	4.8%	95.2%
100	0.02	13.3%	86.7%

Abbreviation: AE = adverse event.

9.4. Analysis Sets

The analysis sets are described in Table 8.

Table 8 Analysis Sets

Set	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.
FAS[1]	The FAS consists of all randomly assigned participants who receive the IP.
PP Set[2]	The PP set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment, do not have influenza or SARS-CoV-2 infection at baseline and post-baseline up to Day 29 (as documented by positive RT-PCR testing result), and have no major protocol deviations and/or prohibited concomitant medication use (documented in the Section 6.5.3) that are prespecified with impacts on the immune response and should be excluded from the PP set.
Safety Set[3]	The safety set consists of all randomly assigned participants who receive the IP.

Set	Description
Solicited Safety Set[4]	The solicited safety set consists of all participants in the safety set who contribute any solicited AR data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; PP = per-protocol.
[1] For the FAS, participants will be analyzed according to the group to which they were randomized.
[2] The PP set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.
[3] The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the vaccination group corresponding to what they actually received.
[4] The solicited safety set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to what they actually received.

9.5. Statistical Methods

9.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, gender, race, ethnicity, height, and weight) and baseline characteristics will be summarized by descriptive statistics for participants in the FAS.

9.5.2. Safety Analyses

All safety analyses are descriptive in nature and will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by study arm. Participants will be included in the vaccination group corresponding to what they actually received. Local solicited reactogenicity analysis will be presented by study group and for each injection content, respectively.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs); unsolicited AEs (including any clinical safety laboratory abnormalities); treatment-related AEs; severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation; vital sign measurements; and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after each vaccination, and with any Grade 3 or higher solicited AR will be summarized. A 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be summarized. Unsolicited AEs will be presented by MedDRA system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for AR Terminology.

The number of events of solicited ARs, unsolicited AEs/SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be reported in summary tables accordingly. Pregnancy outcomes will also be summarized.

Table 9 summarizes the analysis strategy for safety parameters. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Table 9 Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events
Any Solicited AR (overall and by local, systemic)	X
Any Unsolicited AE	X
Any SAE	X
Any Unsolicited MAAE	X
Any Unsolicited AESI	X
Any Unsolicited Treatment-Related AE	X
Any Treatment-Related SAE	X
Any Unsolicited AE Leading to Withdrawal From Study Participation	X
Any Severe Unsolicited AE	X
Any Treatment-Related Severe Unsolicited AE	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; SAE = serious adverse event.
Notes: 95% CI using the Clopper-Pearson method; X = results will be provided.

9.5.3. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP set. If the number of participants in the FAS and PP set differs (defined as the difference divided by the total number of participants in the PP set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the immunogenicity endpoints, the geometric mean of specific antibody titers with corresponding 95% CI at each time point and the geometric mean fold rise (GMFR) of specific antibody titers with the corresponding 95% CI at each post-baseline time point over pre-injection baseline at Day 1 will be provided by treatment arm, with adjustment for baseline antibody titer and other potential covariates, including age group and primary vaccine type. Descriptive summary statistics, including median, minimum, and maximum, will also be provided.

For summarizations of geometric mean titer, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

For mRNA-1010, seroconversion rate from baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point. Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination HAI titer ≥ 1:40 or a pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer.

For mRNA-1273, seroresponse is defined as either: participants with GMFR in nAb or bAb titers of ≥ 4-fold at Day 29 compared to Day 1 in those with baseline titer ≥ LLOQ, or Day 29 titer ≥ 4 × LLOQ if baseline titer is < LLOQ.

The immunogenicity of mRNA-1073 will follow the same rules as mRNA-1010 and mRNA-1273.

Between-group comparisons will be evaluated in terms of immunogenicity endpoints (GMR and SCR/SRR difference) in the PP set and will be specified in the SAP in greater detail.

9.5.4. Exploratory Analyses

Exploratory analyses not addressed in Section 9.5.3 will be described in the SAP before database lock.

9.5.5. Subgroup Analyses

The protocol does not define any formal subgroup analyses; however, age specific analyses might be performed and will be detailed in the SAP.

9.6. Planned Analyses

One IA and final analysis will be conducted in the study. Further details can be found in the SAP.

9.6.1. Interim Analysis

An IA will be performed after all the 550 participants randomized into Group 1 through Group 6 have completed their Day 29 visit assessments and will include the safety and immunogenicity data collected up to Day 29. Either nAb or bAb assay will be used for assessment of immunogenicity. The IA will be performed by a separate team of unblinded programmers and statisticians. The analysis will be presented by vaccination groups. Except for a limited number of Sponsor and CRO personnel who will be unblinded to perform the IA, the study site staff,

investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis.

9.6.2. Final Analyses

The final analysis of all endpoints will be performed after all participants complete Day 181/EoS. Results of this analysis will be presented in a final CSR, including individual listings. The final CSR will include full analyses of all safety and immunogenicity data through Day 181/EoS. For immunogenicity analysis, either nAb or bAb assays will be used in the study.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. APPENDIX 1: Study Governance Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.1.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This

will be documented in a Clinical Study Agreement between the Sponsor, the designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data and/or documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the SAE Hotline, and that those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.1.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the

study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

11.1.4. Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the study site are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

11.1.5. Recruitment Strategy

Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate.

Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site. Advertisements to be used for the recruitment of study participants and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB/IEC.

11.1.6. Informed Consent/Assent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center. All consent documents will be approved by the appropriate IRB. The actual ICF used at each center may differ, depending on local regulations and IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the form being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate.

The participant must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant should also be informed that he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant.

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

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoV.

11.1.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed by the investigator(s), and approved by the relevant IRB(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s) must be provided to the Sponsor before the study is initiated.

Administrative changes to the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigators, and notified to the IRB(s).

11.1.8. Protocol Deviations

Noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations to the Sponsor or its designee. All deviations must be addressed in study source documents and reported to the study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11.1.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, the relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

11.1.10. Sample Retention and Future Biomedical Research

The Sponsor may store samples for the time frame specified in the ICF to achieve study objectives. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity and include humoral and cellular immune assay methodologies to measure responses

to influenza and/or SARS-CoV-2 on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1073 as well as to determine how changes in biomarkers may relate to exposure to mRNA vaccines and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

11.1.11. Safety Oversight

Safety monitoring for the study is described in Section 8.5.

11.1.12. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, EU clinical trial register (eu.ctr), as well as some national registries.

11.1.13. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from Sponsor or qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include onsite inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

11.1.14. Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the study site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHO – Drug Reference List.

11.1.15. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the case report form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts and the signed ICFs are to be included in the investigator's files with the participant's study records.

11.1.16. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.17. Study and Site Closure

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

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

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

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

- Continuation of the study represents a significant medical risk to participants
- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further mRNA-1073 development

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

11.1.18. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

11.2. APPENDIX 2: Contraceptive Guidance

Definitions: Woman of Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

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

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

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

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) with spermicide
- Intrauterine device

- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

11.3. APPENDIX 3: Adverse Events of Special Interest Terms

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

The following table (Table 10) describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per protocol, even when they occur during/following COVID infection.

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

Table 10 Adverse Events of Special Interest

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

Medical Concept	Medical Concept Descriptions/Guidance
	• DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc.; • Increase in serum creatinine by ≥ 0.3 mg/dl (or ≥26.5 μmol/l) within 48 hours; **OR** • Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days
Acute liver injury	• New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.: • >3-fold elevation above the upper normal limit for ALT or AST; **OR** • >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rash • Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions.
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) • Kawasaki's disease • Hemophagocytic lymphohistiocytosis (HLH)
Thrombocytopenia	• Platelet counts < 150×10^9/L (thrombocytopenia) • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR • DOES NOT INCLUDE new onset of chronic arthritic conditions

Medical Concept	Medical Concept Descriptions/Guidance
New onset of or worsening of neurologic disease	• Immune-mediated neurological disorders • Guillain-Barre syndrome • Acute disseminated encephalomyelitis (ADEM) • Peripheral facial nerve palsy (Bell's palsy) • Transverse myelitis • Encephalitis/Encephalomyelitis • Aseptic meningitis • Seizures/convulsions/epilepsy • Narcolepsy/hypersomnia
Anaphylaxis	• Anaphylaxis associated with study drug administration
Other syndromes	• Fibromyalgia • Postural orthostatic tachycardia syndrome • Chronic fatigue syndrome • Myalgic encephalomyelitis • Postviral fatigue syndrome • Myasthenia gravis

Abbreviations: ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019, HELLP = hemolysis, elevated liver enzymes, and low platelet count.

11.4. APPENDIX 4: CDC Working Case Definition of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC working case definition of pericarditis, myocarditis, and myopericarditis to be used in this study is presented in Table 11.

Table 11 CDC Working Case Definition of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Condition	Definition	
Acute myocarditis	**Probable Case**	**Confirmed Case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms:[1]	Presence of ≥ 1 new or worsening of the following clinical symptoms:[1]
	• chest pain, pressure, or discomfort	• chest pain, pressure, or discomfort
	• dyspnea, shortness of breath, or pain with breathing	• dyspnea, shortness of breath, or pain with breathing
	• palpitations	• palpitations
	• syncope	• syncope
	OR, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:	**OR,** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:
	• irritability	• irritability
	• vomiting	• vomiting
	• poor feeding	• poor feeding
	• tachypnea	• tachypnea
	• lethargy	• lethargy
	AND	**AND**
	≥ 1 new finding of	≥ 1 new finding of
	• troponin level above upper limit of normal (any type of troponin)	• Histopathologic confirmation of myocarditis[2]
	• abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[3]	
	• abnormal cardiac function or wall motion abnormalities on echocardiogram	• cMRI findings consistent with myocarditis in the presence of troponin level

Condition	Definition	
	• cMRI findings consistent with myocarditis	above upper limit of normal (any type of troponin)
	AND	**AND**
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings
Acute pericarditis[4]	Presence of ≥ 2 new or worsening of the following clinical features:	
	• acute chest pain[5]	
	• pericardial rub on exam	
	• new ST-elevation or PR-depression on EKG	
	• new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Abbreviations: AV = atrioventricular; CDC = Centers for Disease Control and Prevention; cMRI = cardiac magnetic resonance imaging; COVID-19 = coronavirus disease 2019; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging; mRNA = messenger RNA.

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

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

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

To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

Using either the original or the revised Lake Louise criteria.

https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon.

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

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

Reference: (Gargano et al 2021).

11.5. APPENDIX 5: Protocol Amendment History

11.5.1. Amendment 1 (25 Feb 2022)

Main Rationale for the Amendment:

The purpose of this amendment is to allow people who have received a coronavirus disease 2019 (COVID-19) booster to participate in this study. The booster is now widely available in the United States, and inclusion of individuals who received immunizations beyond the primary series is a protocol change for updated vaccination recommendations. mRNA-1073 is envisioned as an annual vaccine, with the intent to provide continued protection from infections from seasonal influenza viruses and severe acute respiratory syndrome coronavirus 2. Including individuals who have received immunizations beyond the primary series is consistent with the long-term vision for the use of mRNA-1073 as an annual vaccine.

The summary of changes table provided below describes the major changes made in Amendment 1 compared to the original protocol, including the sections modified and the corresponding rationales. As applicable, the synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes From the Original Protocol to Protocol Amendment 1

Section # and Name	Description of Change	Brief Rationale
Global	• Removed passive surveillance from the protocol. Participants will be instructed to contact study sites if they have ILI/COVID-19 symptoms outside the Symptom Reporting eDiary period. • Reduced the frequency during the first month to 1 time per week from 3 to 4 times per week.	• To improve compliance with eDiary reporting: Passive surveillance will be replaced by Symptom Reporting eDiary prompts. • The reduction in frequency is intended to reduce participant fatigue and increase compliance.
Global	• Added 6th arm to study design for Phase 1 to include 100 participants at a CCI of mRNA-1073. • Increased the number of subjects in Arms 2 and 5 from 50 to 100.	• Based on the interim analysis of mRNA-1010 Phase 1/2 showing no immunogenicity dose response, a lower dose is being assessed to support dose selection of mRNA-1073. Arms 2 and 5 increased in size improve

Section # and Name	Description of Change	Brief Rationale
		comparability across treatments.
Sections 1.1 (Synopsis), 2.1.2 (mRNA-1273), and 4.3 (Choice of Vaccine Dose)	• Updated mRNA-1273 booster guidance to individuals 18 years of age and older.	• The FDA has authorized for emergency use the administration of a single booster dose ([redacted]) of mRNA-1273 vaccine in individuals 18 years of age and older.
Sections 1.1 (Synopsis), 2.1.2 (mRNA-1273), and 4.3 (Choice of Vaccine Dose)	• Added: In January 2022, the US FDA approved the Biologics License Application (BLA) for SPIKEVAX (mRNA-1273) to prevent COVID-19 in individuals 18 years of age and older.	• This updated BLA approval was added to the protocol.
Sections 1.1 (Synopsis), 4.1 (General Design), 5.1 (Inclusion Criteria), and 9.3 (Sample Size Determination)	• Updated inclusion criteria (inclusion criterion 7) to allow for a COVID-19 booster vaccine and clarify that the last COVID-19 vaccine received (from the primary series or booster) must be ≥ 120 days prior to the randomization visit (or less per local guidance).	• Because this amendment is allowing participants who have received a COVID-19 booster, this updated verbiage specifies that the last vaccine (primary series or booster) must be ≥ 120 days prior to the randomization visit (or less per local guidance).
Sections 1.1 (Synopsis) and 5.2 (Exclusion Criteria)	• Deleted exclusion criterion 15 (participant has received a booster dose of a COVID-19 vaccine) and renumbered the criteria.	• Per the main rationale of the amendment, this exclusion criterion was removed to allow study participants who have received a booster dose of a COVID-19 vaccine to participate in this study.
Sections 1.1 (Synopsis), 4.1 (General Design), 5.2 (Exclusion Criteria),	• Exclusion criteria 14 was changed to the following: Participant has known history of SARS-CoV-2 infection within ≤ 90 days.	• The time from known history of SARS-CoV-2 infection was reduced from ≤ 180 days to ≤ 90 days to

Section # and Name	Description of Change	Brief Rationale
and 9.3 (Sample Size Determination)		allow study participants who may have been infected during the Omicron wave.
Sections 1.1 (Synopsis), 4.1 (General Design), and 6.2 (Randomization and Blinding)	• Added: Randomization for Phase 2 will be stratified by receipt of a COVID-19 booster (yes or no) instead of receipt of prior SARS-CoV-2 vaccine that is mRNA based.	• Per the main rationale of the amendment to allow study participants who have received a booster dose of a COVID-19 vaccine, this change in randomization scheme for Phase 2 is more appropriate.
Sections 1.1 (Synopsis) and 2.2.2 (Clinical Studies)	• Deleted reference to a substudy to mRNA-1010-P101 in the background sections.	• This substudy was cancelled and is no longer applicable.
Sections 1.1 (Synopsis) and 5.2 (Exclusion Criteria)	• Exclusion criterion 13 was updated to the following: Participant has had close contact to someone with SARS-CoV-2 infection or COVID-19 as defined by the US CDC in the past 10 days prior to the Screening Visit.	• This change was made for clarity and to harmonize across Sponsor programs.
Section 2.2.2 (Clinical Studies)	• Background information was added highlighting that an amendment is planned (for a separate study, mRNA-1010-P101) to assess 6.25 µg and 12.5 µg dose levels of mRNA-1010 as well as 25 µg mRNA-1010 and an active comparator in the Phase 2 Extension portion of the study	• This detail was added to update the background of the clinical program pertaining to doses of mRNA-1010 under investigation.
Section 2.2.1 (Nonclinical Studies)	• Additional nonclinical study background information provided regarding test article related	• Test article related clinical pathology and cytokine changes were generally

Section # and Name	Description of Change	Brief Rationale
	clinical pathology and cytokine changes.	reversed or reversing by the end of the 2-week recovery period.
Sections 2.3.3 (Overall Benefit/Risk Conclusion) and 4.3 (Choice of Vaccine Dose)	• Added mRNA-1010 immune response data to support benefit/risk discussion.	• IA data from the mRNA-1010-P101 study showing tolerability profile and similar levels of anti-hemagglutination antibody responses across doses support the selection of mRNA-1073 at CCI [redacted] dose levels in Phase 1.
Section 8.4.3 (Solicited Adverse Reactions)	• Modified Grade 2 and Grade 3 solicited adverse reaction descriptions for injection site pain, axillary swelling or tenderness ipsilateral to the side of injection, and headache (Table 8). All of these Grade 2 solicited adverse reactions are now described as "some interference with activity" and all of these Grade 3 solicited adverse reactions are now described as "prevents daily activity."	• These grade definitions were modified to more clearly differentiate between Grade 2 and Grade 3 injection site pain, axillary swelling or tenderness ipsilateral to the side of injection, and headache solicited adverse reactions.
Global	• Editorial changes.	• Minor editorial changes throughout based on amendment updates.

Abbreviations: CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; eDiary = electronic diary; FDA = Food and Drug Administration; HAI = hemagglutination inhibition; IA = interim analysis; ILI = influenza-like illness; mRNA = messenger RNA; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; US = = United States.

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