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ModernaTX, Inc.

Protocol mRNA-1020-P101

A Phase 1/2, Randomized, Observer-Blind, Dose Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1020 and mRNA-1030 Candidate Seasonal Influenza Vaccines in Healthy Adults

STATISTICAL ANALYSIS PLAN

SAP Version: 2.0
Version Date of SAP: 12-Jul-2022

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	29-March-2022	Initial Version
2.0	12-July-2022	• Added between-group comparison for GMTR using ANCOVA. • Added between-group SCR difference using Miettinen-Nurminen method. • Changed D29 visit window for PP Set to -7/+14 days • Changed the 'Analysis Visit Window' table. • Updated Medical Lead team member

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
BMI	body mass index
BUN	blood urea nitrogen
BP	blood pressure
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DBP	data blinding plan
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
IA	interim analysis
ILI	influenza-like illness
IP	investigational product
IST	internal safety team
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MN	microneutralization
mRNA	messenger ribonucleic acid
NA	neuraminidase
NAI	neuraminidase inhibition

Abbreviation	Definition
NH	Northern Hemisphere
NP	nasopharyngeal
PP	per-protocol
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SoE	schedule of events
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHO Drug Global	World Health Organization drug dictionary

1 INTRODUCTION

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1020-P101, is based on the protocol dated 16-Feb-2022, and the electronic case report form (eCRF), dated 21-Mar-2022. SAP will be based on the latest protocol and eCRF and will be updated as necessary.

In addition to the information presented in the SAP section of the protocol (Section 9), which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations.

This is a Phase 1/2, randomized, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1020 and mRNA-1030 candidate seasonal influenza vaccines in healthy adults 18 to 75 years of age.

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

In this document, study vaccination, injection of investigational product (IP) / investigational vaccine, and injection are used interchangeably.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and reactogenicity of mRNA-1020, mRNA-1030, and mRNA-1010
- To evaluate the humoral immunogenicity of mRNA-1020, mRNA-1030, and mRNA-1010 against vaccine-matched influenza A and B strains at Day 29

2.2 Secondary Objectives

- To evaluate the humoral immunogenicity of mRNA-1020, mRNA-1030, and mRNA-1010 against vaccine-matched influenza A and B strains at all evaluable humoral immunogenicity time points

2.3 Exploratory Objectives

The exploratory objectives (may be performed) are the following:

- To evaluate the humoral immunogenicity against vaccine-mismatched influenza A and B strains
- To evaluate cellular immunogenicity in a subset of participants
- To further characterize antibody responses, for example, Fc-mediated function, avidity, or epitope specificity
- To assess the occurrence of clinical influenza in study participants and characterize their immune response to infection and viral isolates
- Sample collection to perform passive transfer studies in preclinical animal models

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Safety

- Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period post-vaccination
- Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period post-vaccination
- Frequency of any serious adverse events (SAEs), adverse events of special interest (AESIs), medically attended adverse events (MAAEs), and AEs leading to withdrawal from Day 1 through Day 181/end of study (EoS)
- Safety laboratory abnormalities through 7 days post-vaccination

Immunogenicity

- Geometric mean titer (GMT) and geometric mean fold rise (GMFR) at Day 29 compared with Day 1 (baseline) and 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-hemagglutinin (HA) antibodies measured by hemagglutination inhibition (HAI) assay
- GMT and GMFR of anti-neuraminidase (NA) measured by neuraminidase inhibition (NAI) assay at Day 1 and Day 29 and percentage of participants with a change in the Day 29 titer of at least 2-/3-/4-fold rise, defined as ≥ 2-/3-/4-fold of

the lower limit of quantification (LLOQ) if the Day 1 titer is < LLOQ; or ≥ 2-/3-/4-fold of the Day 1 titer if the Day 1 titer is ≥ LLOQ

3.2 Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- GMT and GMFR of anti-HA or anti-NA antibodies as measured by HAI, NAI, and/or MN assays at all evaluable humoral immunogenicity time points compared with Day 1 (baseline)

3.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- GMT and GMFR of anti-HA or anti-NA antibodies as measured by HAI, NAI, and/or MN assays against vaccine-mismatched strains compared with Day 1 (baseline)
- 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 T-cells and B-cells after vaccination
- Frequency, specificities, or other endpoints to be determined, for the further characterization of antibody responses
- Frequency of clinical influenza and assessment of immune responses in participants with clinical influenza
- Transfer of human sera into mice with subsequent influenza virus challenge to observe protection from morbidity and mortality conferred by NA-specific antibodies

4 STUDY DESIGN

4.1 Overall Study Design

This is a Phase 1/2, randomized, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1020 (CCI [redacted]) and mRNA-1030 (CCI [redacted]) in healthy adults 18 to 75 years of age. Enrollment in study arms will proceed in parallel with randomization of all dose levels of mRNA-1020 and mRNA-1030 (Study Arms 1 to 6), the mRNA-1010

Comparator Arm (Study Arm 7), and the Flublok Comparator Arm (Study Arm 8). The study will randomize approximately 70 healthy adult participants into each study arm with a balanced age group representation stratified approximately 1:1 into age groups of 18 to < 50 years of age and ≥ 50 to ≤ 75 years of age.

The vaccines to be tested contain mRNAs encoding for the surface glycoproteins of the strains recommended by the WHO for 2021/22 NH cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019(H1N1)pdm09
- A/Cambodia/e0826360/2020(H3N2)
- B/Washington/02/2019 (B/Victoria lineage)
- B/Phuket/3073/2013 (B/Yamagata lineage)

All participants will participate in a screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and follow-up period (up to 6 months after vaccination). Approximately 560 participants will be randomized to receive a single dose of either one of the 2 next-generation candidate vaccines (mRNA-1020 or mRNA-1030) at different dose levels, a single dose of the first-generation candidate vaccine (mRNA-1010), or Flublok, a licensed enhanced seasonal influenza vaccine comparator (8 study arms total). Three different dose levels (CCI [redacted]) of CCI [redacted] (mRNA-1020), 3 different dose levels (CCI [redacted]) of CCI [redacted] (mRNA-1030), and a single dose level of mRNA-1010 (50 µg total mRNA) will be assessed. The target number of participants in each arm and the randomization ratio can be found in Table 1. The study schema is illustrated in Figure 1.

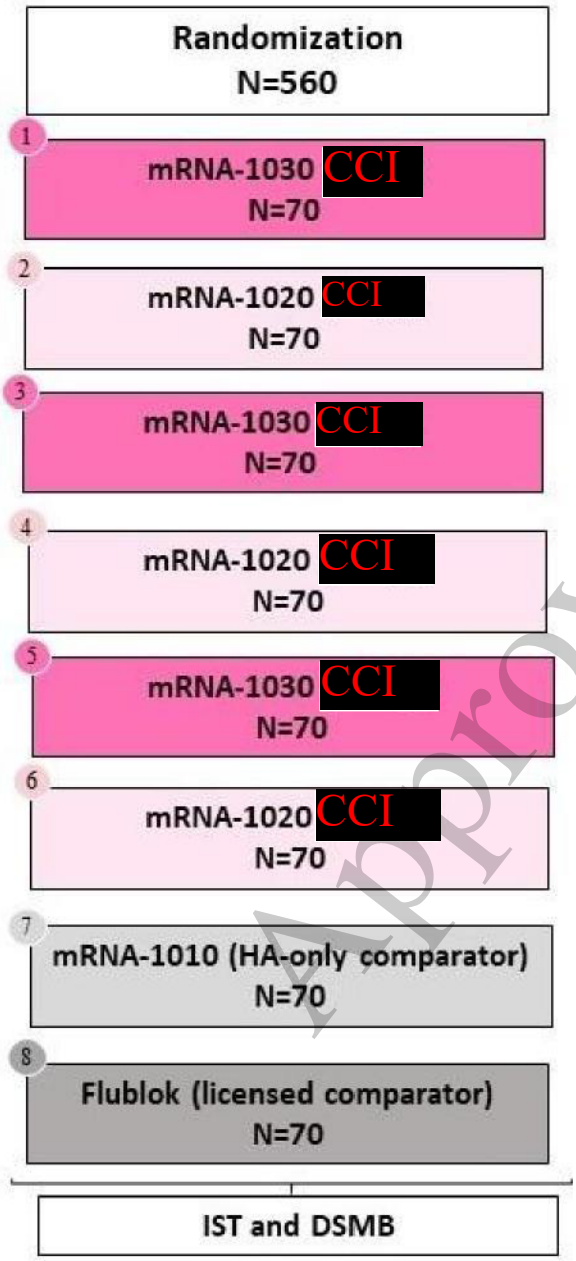
This study is designed as an observer-blind study. Participants in Vaccination Groups 1, 3, and 5 will receive mRNA-1030 vaccine and participants in Groups 2, 4, and 6 will receive mRNA-1020 vaccine. mRNA-1010 and Flublok will be used as comparators for descriptive comparisons of safety and immunogenicity.

Table 1 Study Arms and Dose Levels

Vaccination Group	Group Name	Antigen(s)	CCI	CCI	CCI	CCI
1	**mRNA-1030**	HA+NA				
2	**mRNA-1020**	HA+NA				
3	**mRNA-1030**	HA+NA				
4	**mRNA-1020**	HA+NA				
5	**mRNA-1030**	HA+NA				
6	**mRNA-1020**	HA+NA				
7	**mRNA-1010** (HA only comparator)	HA only	**50 µg**			
8	**Flublok** (active comparator)	HA only	**180 µg**			
Total						

Abbreviations: HA = hemagglutinin; mRNA = messenger RNA; NA = neuraminidase.

Figure 1 Study Schema



Abbreviations: DSMB = data safety monitoring board; HA = hemagglutinin; IST = internal safety team; V = visit.

4.2 Statistical Hypotheses

No formal hypotheses will be tested for this study.

4.3 Sample Size and Power

The sample size for this trial 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 dose levels of mRNA-1020 or mRNA-1030.

A total of approximately 560 participants will be randomly assigned to receive mRNA-1020, mRNA-1030, mRNA-1010, or Flublok. Among those ~560 participants, 70 participants will be randomized into each vaccination group. Details regarding the number of participants in each vaccination group and the randomization ratio are presented in Table 1. With 70 participants in each group receiving the IP, there is an approximately 76% probability to observe at least 1 participant with an AE if the true incidence of the AE is 2%; if the true incidence rate is 4%, then the probability to observe an AE is approximately 94%.

4.4 Randomization

Approximately 560 participants will be randomized in a 1:1:1:1:1:1:1:1 ratio to receive either mRNA-1020 CCI mRNA-1020 CCI, mRNA-1020 CCI, mRNA-1030 CCI mRNA-1030 CCI, mRNA-1030 CCI, mRNA-1010 50 µg, or Flublok 180 µg, with approximately 70 healthy adult participants randomly assigned to each vaccination group. Randomization will be stratified by age (18 to < 50 years versus ≥ 50 to ≤ 75 years) and will be balanced across the 2 age groups within each vaccination group.

4.5 Blinding and Unblinding

This study 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 certain exceptions; please refer to Section 9.1 of the protocol and Data Blinding Plan (DBP) for details.

5 ANALYSIS POPULATIONS

5.1 Randomization Set

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

5.2 Full Analysis Set (FAS)

The FAS consists of all randomly assigned participants who receive the IP. Participants will be analyzed according to the group to which they were randomized.

5.3 Per-Protocol (PP) Set

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 infection at baseline through Day 29 (as documented by PCR testing), and have no major protocol deviations that impact the immune response. 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 vaccination group to which they were randomized.

Participants compliant with the timing of immunogenicity blood sampling are required to have a baseline assessment, at least one post-injection assessment, and a Day 29 assessment that is within 21 days to 42 days after injection (-7 / +14 days of Day 29).

Participants with a dosing error will be considered as having a protocol deviation. However, the determination of whether to include/exclude participants from the PP Set due to a dosing error will be based on the dosage difference (in µg) between the actual dose received and the randomized dose. The PP Set exclusion criteria for participants with dosing error are described in Table 2. For the mRNA-1020 and the mRNA-1030 arms, acceptable dosing deviation from the randomized dose is up to CCI [redacted]. For the mRNA-1010 active comparator, participants who are randomized to the active comparator arm but received less than CCI [redacted] of the active comparator or any amount of mRNA-1020, mRNA-1030, or Flublok active comparator will be excluded from the PP Set. For the Flublok active comparator, participants who are randomized to the active comparator arm but received less than CCI [redacted] of the active comparator or any amount of mRNA-1020, mRNA-1030, or mRNA-1010 active comparator will be excluded from the PP Set.

Table 2 PP Set Exclusion Criteria for Dosing Errors

Actual Dose Received	Randomized Dose: mRNA-1020			mRNA-1030			mRNA-1010 (active comparator) [1]	Flublok (active comparator) [2]
mRNA-1020								
CCI		Y	Y	Y	Y	Y	Y	Y
	Y		Y	Y	Y	Y	Y	Y
	Y	Y		Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y
		Y	Y	Y	Y	Y	Y	Y
		Y	Y	Y	Y	Y	Y	Y
	Y		Y	Y	Y	Y	Y	Y
	Y		Y	Y	Y	Y	Y	Y
	Y	Y		Y	Y	Y	Y	Y
	Y	Y		Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y
mRNA-1030								
CCI	Y	Y	Y		Y	Y	Y	Y
	Y	Y	Y	Y		Y	Y	Y
	Y	Y	Y	Y	Y		Y	Y
	Y	Y	Y		Y	Y	Y	Y
	Y	Y	Y		Y	Y	Y	Y
	Y	Y	Y	Y		Y	Y	Y
	Y	Y	Y	Y		Y	Y	Y
	Y	Y	Y	Y	Y		Y	Y
	Y	Y	Y	Y	Y		Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y
mRNA-1010 (active comparator) [1]	Y	Y	Y	Y	Y	Y		Y
Flublok (active comparator) [2]	Y	Y	Y	Y	Y	Y	Y	

Note: Y = Excluded from PP Set.

5.4 Safety Set

The Safety Set consists of all randomly assigned participants who receive the IP. 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 according to the following rules:

- mRNA-1030 CCI group: If the received dose of mRNA-1030 is CCI
- mRNA-1030 CCI group: If the received dose of mRNA-1030 is CCI
- mRNA-1030 CCI group: If the received dose of mRNA-1030 is CCI
- mRNA-1020 CCI group: If the received dose of mRNA-1020 is CCI
- mRNA-1020 CCI group: If the received dose of mRNA-1020 is CCI
- mRNA-1020 CCI group: If the received dose of mRNA-1020 is CCI
- mRNA-1010 (HA only comparator) group: If the received dose of mRNA-1020/ mRNA-1030/Flublok is 0 µg and mRNA-1010 >0 µg
- Flublok (active comparator) group: If the received dose of mRNA-1020/mRNA-1030/mRNA-1010 is 0 µg and Flublok >0 µg

5.5 Solicited Safety Set

The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. 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 as shown in Section 5.4.

6 STATISTICAL ANALYSIS

6.1 Planned Analyses

6.1.1 Interim Analysis (IA)

An interim analysis will be performed after participants have completed the Day 29 Visit. All data relevant to the IA through the Day 29 Visit will be cleaned (i.e., data that are as clean as possible).

The IA will be performed by a separate team of unblinded statisticians and programmers. Except for a limited number of Sponsor and CRO personnel who will be unblinded to perform the IA, the study site staffs, Investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis.

6.1.2 Internal Safety Team (IST) Review

A blinded IST will comprise Sponsor physicians. The IST will conduct a scheduled review of safety data after approximately 96 participants (approximately 12 per study arm) have completed the Day 8 visit as well as ad hoc safety data review if requested by the study medical monitor and the study team.

6.1.3 Data Safety Monitoring Board (DSMB) Review

The DSMB, composed of external/independent participant matter experts, will conduct unblinded reviews of safety data on an ad hoc basis if any pause rule is met or as otherwise requested by the study team and /or IST. The DSMB will review unblinded IA results and make recommendations to sponsor.

6.1.4 Final Analysis

The final analysis of safety, reactogenicity, and immunogenicity will be performed after all participants have completed all planned study procedures. The results of this analysis will be presented in a final clinical study report, including individual listings.

6.2 General Considerations

The Schedules of Events (SoE) are provided in Table 1 of the protocol Section 1.3.

General considerations for analyses will be applied to this study, unless otherwise specified. All analyses will be performed by treatment arm, unless otherwise specified. Statistical outputs (tables, figures, listings, and datasets) will refer to study participants as participants and will use vaccination, injection of IP and injection interchangeably. All

analyses will be conducted using SAS Version 9.4. All table data will have a corresponding listing.

6.2.1 Data Precision

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

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that vaccination group within the analysis set of interest, unless otherwise specified.

6.2.2 Statistics for Continuous and Categorical Variables

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

Categorical variables will be summarized using frequencies and percentages.

6.2.3 Baseline

Baseline results for laboratory measurements, vital signs, immunogenicity, and nasopharyngeal (NP) swab tests will be defined as the last recorded non-missing value prior to study vaccine administration.

6.2.4 Reference Start Date and Study Day

The reference start date is used as the time point from which the study day is calculated. Study days prior to the reference start date will be negative, while study days after the reference start date are positive.

The reference start date is the date of study vaccine administration.

Study day will be calculated as follows:

- Study day prior to vaccination will be calculated as:

  date of assessment/event – the reference start date

- Study day on or after the date of vaccination will be calculated as:

  date of assessment/event – the reference start date + 1.

An assessment/event date on the reference start date will be study day 1.

6.2.5 Handling Non-Quantifiable Antibody Values

For calculation regarding antibody levels/titers, antibody values reported as below 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. Missing results will not be imputed.

6.2.6 Analysis Periods for Safety Analyses

The following analysis periods for safety analyses will be used in this study:

- 7 days following vaccination: this period includes the day of vaccination and 6 subsequent days. This analysis period will be used for solicited local and systemic ARs that occur during this time.
- 28 days following vaccination: this period includes the day of vaccination and 27 subsequent days. This analysis period will be used for unsolicited AEs.
- Overall period: this analysis period starts on Day 1 and continues through the earliest of the following: Day 181/study completion, discontinuation from the study, or death.

6.2.7 Unscheduled Visits and Visit Windowing Rules

Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment values.
- In the derivation of max/min on-treatment values and max/min change from baseline values for safety analyses.
- In individual participant data listings as appropriate.

The analysis visit windows for protocol-defined visits are provided in Appendix B.

6.2.8 Handling Missing and Incomplete Data

- Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., < 0.1), the numeric values will be replaced by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (e.g., > 3000), the numeric values will be replaced by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless otherwise specified.

6.2.9 Age and Vaccination Groups

Age groups:

The following age groups will be used for summary purposes:

- Overall
- Age: ≥ 18 to < 50 years
- Age: ≥ 50 to ≤ 75 years

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1030 CCI
- mRNA-1020 CCI
- mRNA-1030 CCI
- mRNA-1020 CCI
- mRNA-1030 CCI
- mRNA-1020 CCI
- mRNA-1010 50 µg
- Flublok 180 µg

All analyses and data summaries/displays will be provided by vaccination group (and then by age group) using appropriate analysis population, unless otherwise specified.

6.2.10 Adjustment for Covariates

The estimates of GMFR with 95% CIs will be calculated based on analysis of covariance (ANCOVA) model adjusted for baseline titer, age group and /or other covariates. Antibody titers are analyzed using $\log_2$ titers or $\log_2$ fold rise and back transformed to estimate GMFRs with 95% CIs. After transformation, the data tend to be normally distributed.

6.3 Background Characteristics

The following description of background characteristics analyses will be applied to this study, unless otherwise specified.

6.3.1 Participant Disposition

The number and percentage of participants in the following categories will be summarized by randomized vaccination group and then further by age group as defined in Section 6.2.9 based on Randomization Set:

- Randomization Set
- Full Analysis Set (FAS)
- Per-protocol (PP) Set
- Safety Set
- Solicited Safety Set

The percentage will be based on participants in that vaccination group within the Randomization Set. A summary of reasons for participants who are in the Randomization Set but excluded from PP Set will also be provided. Listing of analysis sets will be provided based on the Randomization Set.

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

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

The percentage of participants who screen failed will be based on the number of participants screened. The percentage of participants for each reason for screen failure will be based on the number of participants who screen failed. For screened failure participants, age (years), as well as sex, race, ethnicity, and reasons for screen failure will be presented in a listing.

The number and percentage of participants in each of the following disposition categories will be summarized by vaccination group (and then by age group) based on the Randomization Set:

- Received injection
- Completed study
- Discontinued from the study and the reason for discontinuation

A participant disposition listing will be provided, including informed consent date, injection date, date of study completion, date of study discontinuation, with reasons for discontinuation.

A participant who completed Day 181/EoS (Month 6 visit), defined as 6 months after the study vaccination on Day 1, is considered to have completed the study.

6.3.2 Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of participants will be provided for categorical variables such as gender, race, and ethnicity. The summaries will be presented by vaccination group and overall based on the Randomization Set, FAS, PP Set, and Safety Set. If the Safety Set differs from the Randomization Set (e.g., participants randomized but not received any study vaccination or participants received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomization Set. Summary of RT-PCR SARS-CoV-2 results at baseline, baseline RT-PCR Influenza Results and Seasonal Influenza Vaccine since Sep 2021.

Listing of demographics and baseline characteristics will be provided based on the Randomization Set.

6.3.3 Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOCs will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in total of each type of vaccination group/overall group and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.3.4 Prior and Concomitant Medications

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

The number and percentage of participants using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after the injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination groups as follows:

- Any concomitant medications and non-study vaccination within 7 days post-injection
- Any concomitant medications within 28 days post-injection
- Any non-study vaccination within the period starting 28 Days before IP Injection and through Day 181/EoS
- Any Seasonal influenza vaccine from September 2021 through Day 181/EoS
- Any Covid-19 Vaccine before the IP Injection and through Day 181/EoS
- Antipyretic or analgesic medication within 28 days post-injection

A summary table of concomitant medications and non-study vaccination that continued or was newly received on the date of injection through 28 days post-injection will be provided by PT in descending frequency in the total group.

Medications taken to prevent or treat pain or fever within 7 days after injection will be collected in the electronic diary (eDiary), and summaries will be provided based on the Solicited Safety Set by vaccination group (and then by age group) as defined in Section 6.2.9.

Prior, concomitant, post medications, and non-study vaccination will be presented in a listing. Medications taken to prevent or treat pain or fever will also be presented in a listing.

Concomitant procedures will be presented in a listing.

6.3.5 Study Exposure

Study IP administration data will be presented in a listing. Participants with dosing error will be presented in a listing.

Study duration will be summarized from randomization and from the injection based on the Safety Set.

6.3.6 Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by vaccination group (and then by age group) based on the Randomization Set.

Major protocol deviations will be presented in a listing.

If the protocol deviations (PDs) are classified as Important/Non-Important', then Important means Major and Non-Important means Minor.

6.3.7 COVID-19 Impact

A listing will be provided for the impact of coronavirus disease 2019 (COVID-19) on the execution of the study.

6.4 Safety Analysis

All safety analyses 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 vaccination group and by age group. Participants will be included in the vaccination group corresponding to what they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including the following:

- solicited local and systemic ARs
- unsolicited AEs (including any clinical safety laboratory abnormalities)
- treatment-related AEs
- severe AEs
- SAEs
- AESIs
- MAAEs
- AEs leading to withdrawal from study participation
- vital sign measurements
- physical examination findings

Unsolicited AEs will be coded by system organ class (SOC) and preferred term (PT) according to MedDRA. Solicited ARs will be coded according to the MedDRA for AR terminology.

All table data will have a corresponding listing. Safety phone calls data will be provided in a listing. Deaths will be provided in a listing.

6.4.1 Unsolicited Adverse Events

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 (i.e., for the 7 days after the injection of IP).

Only treatment-emergent AE (TEAE) will be included in the analysis. A TEAE is defined as any event occurring during the study not before exposure to study vaccine or any event already present that worsens in intensity or frequency after exposure to study vaccine.

AEs will also be evaluated by the investigator for MAAE and AESI. An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner (HCP). An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor are required. The AESIs for this study are listed in APPENDIX 3 of the protocol Section 11.3.

Unsolicited AEs within 28 days after vaccination will be summarized by vaccination group. Unsolicited SAE, unsolicited AESI, unsolicited MAAE, and unsolicited AE leading to withdrawal from the study up to 28 days after vaccination and overall period will be summarized by vaccination group. See Section 6.2.9 and Section 6.2.6 for definitions of analysis groups and analysis period respectively.

All summary tables (except for the overall summary of AEs) for unsolicited TEAEs will be presented by SOC and/or PT, and by SOC and PT and severity, with counts of participants included. SOCs will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency of total in each vaccine type group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity in the summaries by severity, if participants reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of participants in the Safety Set within each vaccination group.

6.4.1.1 Incidence of Unsolicited Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of participants who experience the following within 28 days after vaccination (See Section 6.2.6 for safety analysis periods) will be presented:

- Any unsolicited TEAEs (See Section 6.2.6 for study periods)
- Any unsolicited serious TEAEs
- Any unsolicited fatal TEAEs
- Any unsolicited medically attended TEAEs
- Any unsolicited treatment-emergent AESI

- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs

The table will also include number and percentage of participants with unsolicited TEAEs within 28 days after vaccination that are treatment-related in each of the above categories.

In addition, separate listings containing individual participant AE data for unsolicited TEAEs, unsolicited TEAEs leading to withdrawal from study participation, unsolicited AESI, and unsolicited medically attended TEAEs will be provided. Unsolicited treatment-related TEAEs, unsolicited severe TEAEs, unsolicited treatment-related severe TEAEs, unsolicited serious treatment-related AEs, unsolicited treatment-related medically attended TEAEs, unsolicited adverse events leading to death, and unsolicited TEAEs for participants with influenza or SARS-CoV-2 infection will also be provided in corresponding listings.

6.4.1.2 TEAEs by System Organ Class and Preferred Term

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

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All unsolicited TEAEs leading to withdrawal from study participation
- All unsolicited severe TEAEs
- All unsolicited severe TEAEs that are treatment-related
- All unsolicited treatment-emergent AESIs
- All unsolicited medically attended TEAEs
- All unsolicited medically attended TEAEs that are treatment-related

6.4.1.3 TEAEs by Preferred Term

Summary tables of all unsolicited TEAEs within 28 days after vaccination will be provided by preferred term. PTs will be sorted in a descending order according to the frequency in total in each type of vaccination group.

6.4.1.4 TEAEs by System Organ Class, Preferred Term, and Severity

The following summary tables of TEAEs within 28 days after vaccination will be provided by SOC, PT, and maximum severity (mild, moderate, severe) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.4.2 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
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Medically important event

The overall summary of unsolicited TEAEs in Section 6.4.1.1 will include the following:

- Any unsolicited serious TEAEs
- Any unsolicited serious treatment-related TEAEs

The following summary tables of unsolicited serious TEAEs within 28 days and overall period will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited serious TEAEs
- All unsolicited serious TEAEs that are treatment-related

6.4.3 Solicited Adverse Reactions

Solicited ARs refers to selected signs and symptoms occurring after vaccination during a specified post-vaccination follow-up period (day of vaccination and 6 subsequent days). The solicited ARs are recorded daily by the participant in the eDiary.

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 participant should notify the site to provide an end date to close out the event on the Reactogenicity page of the eCRF. If the participant reported an event after the solicited period (i.e., after Day 7). it should be recorder as an AE on the AE page of the eCRF.

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

Analyses of solicited ARs will be provided by vaccination group based on the Solicited Safety Set. All solicited ARs (overall, local, and systemic) reported during the 7-day follow-up period after vaccination will be summarized. A 2-sided 95% CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

- The number and percentage of participants who reported solicited local ARs and solicited systemic ARs during the 7-day follow-up period after injection or persisting beyond 7 days after injection will be tabulated by vaccination group and toxicity grade.
- The number and percentage of participants who reported each individual solicited AR will also be summarized by vaccination group, toxicity grade, and day of reporting based on the eDiary. Analyses will be displayed for each age group.

A two-sided 95% CI using the Clopper-Pearson method will be provided for the percentage of participants who reported any solicited AR, any solicited local AR, or any solicited systemic AR.

The onset of individual solicited ARs is defined as the time point after injection at which the respective solicited AR first occurred. The number and percentage of participants with onset of individual solicited AR within 7 days will be summarized by vaccination group and onset day relative to injection day (Day 1). Analyses will be displayed for each age group.

The number of days reporting each solicited AR will be summarized descriptively and categorically for the following time windows (1-2 days, 3-4 days, 5-6 days, and 7 days) by vaccination group (and then by age group).

The number of days will be calculated as the day(s) the solicited AR is reported within 7 days of injection including the day of injection, no matter if it is intermittent or continued.

Solicited local, solicited systemic ARs and solicited ARs persisting beyond 7 days collected in the eDiary will be provided in corresponding listings, and the maximum toxicity grade from eDiary will be presented. Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 7 of the protocol Section 8.4.3. modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b).

6.4.4 Clinical Laboratory Evaluations

Safety laboratory testing will include hematology and serum chemistry.

For continuous hematology and serum chemistry parameters, the observed values and changes from baseline will be summarized at each time point by vaccination group and then by age group as defined in Section 6.2.9.

Summary of Grade 3+ laboratory abnormalities by visit and toxicity grades will be provided by vaccination group and then by age group as defined in Section 6.2.9.

Hematology and chemistry toxicity grades will be summarized using a shift table from baseline to Day 8 by vaccination group.

All laboratory test results will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the toxicity grading criteria (Grade 3 or higher) in Appendix E in any safety laboratory (hematology and serum chemistry) will be listed separately.

A pregnancy test will be performed on all female participants of childbearing potential at the Screening Visit and before vaccine administration on Day 1 via point-of-care urine, and as needed at unscheduled visits (urine or blood pregnancy test based on the investigator's discretion).

The pregnancy test results will be listed.

6.4.5 Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures (BP), heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values that are outside the reference ranges will be flagged in the data listing. The abnormalities

meeting the toxicity grading criteria (Grade 3 or higher) in Appendix F in any vital sign measurement will be listed separately.

Observed values and changes from pre-vaccination (baseline) to post-vaccination at Day 1 for all vital sign measurements will be summarized by vaccination group and then by age group as defined in Section 6.2.9.

Shift from baseline in the toxicity grades to post-vaccination result at Day 1 will also be summarized by vaccination group and then by age group.

6.4.6 Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Table 1 of the protocol Section 1.3.

The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities.

Any clinically significant finding identified during a study visit before administration of study vaccine will be recorded in the participant's medical history eCRF.

Any clinically significant finding identified during a study visit after administration of study vaccine will be reported as an MAAE.

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

Summary tables or listing will not be provided for physical examinations.

6.4.7 Electrocardiogram (ECG)

12-lead ECG measurements will be recorded after 10 minutes of supine rest at Visit 1/Day 1 prior to vaccination. Summary table or listing will not be provided for ECG.

6.5 Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Set and will be performed by vaccination group and by age group.

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% for each age

group, supportive analyses of immunogenicity may be conducted using the FAS. The supportive analysis is required if the condition is met.

The GMT and geometric mean (GM) level will be calculated using the following formula:

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

The GMFR measures the changes in immunogenicity titers or levels within participants. The GMFR will be calculated using the following formula:

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 2^{\left\{\frac{\sum_{i=1}^{n} log_2(v_{ij}) - log_2(v_{ik})}{n}\right\}}$$

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity titers or levels for participant i at time points j and k, $j \neq k$.

The 95% CIs for GMT and GMFR will be calculated based on the t distribution of the log-transformed values then back transformed to the original scale for presentation, unless otherwise specified. Reverse cumulative distribution plot will be generated.

The model-based GM titer will be estimated based on an analysis of covariance (ANCOVA) model. In the ANCOVA model, the log-transformed antibody titer at a post baseline timepoint (Day 29) are treated as a dependent variable, with the treatment group as an explanatory variable and the log-transformed baseline antibody titer as a covariate, adjusting for the stratification factor(s) as appropriate, that is, age groups (18 to 49 years old, and 50 to 75 years old of age).

The GMT will be estimated by the geometric least square mean (GLSM) from the ANCOVA model for each treatment group and corresponding 95% CI will be provided.

For each pair of between-group comparison specified in Table 3, the GMR (ratio of GMTs) between the two treatment groups in each pair will be estimated from the ANCOVA model, with 95% CI provided accordingly.

For each pair of between-group comparison specified in Table 3, the difference of seroconversion rate (SCR) between the two treatment groups in each pair at Day 29 will be provided, with 95% CI estimated using Miettinen-Nurminen method.

Table 3 Exploratory Between-Group Immunogenicity Comparisons

Treatment Group	Group #1	Group #2	Group #3	Group #4	Group #5	Group #6	Group #7	Group #8
Group #1	NA	NA	NA	NA	NA	NA	NA	NA
Group #2	NA	NA	NA	NA	NA	NA	NA	NA
Group #3	#3 vs. #1	#3 vs. #2	NA	NA	NA	NA	NA	NA
Group #4	#4 vs. #1	#4 vs. #2	#4 vs. #3	NA	NA	NA	NA	NA
Group #5	#5 vs. #1	#5 vs. #2	#5 vs. #3	#5 vs. #4	NA	NA	NA	NA
Group #6	#6 vs. #1	#6 vs. #2	#6 vs. #3	#6 vs. #4	#6 vs. #5	NA	NA	NA
Group #7	#7 vs. #1	#7 vs. #2	#7 vs. #3	#7 vs. #4	#7 vs. #5	#7 vs. #6	NA	NA
Group #8	#8 vs. #1	#8 vs. #2	#8 vs. #3	#8 vs. #4	#8 vs. #5	#8 vs. #6	#8 vs. #7	NA

Note: The 8 treatment groups can be found in Table 1 and the order might be re-arranged for easier reference.

6.5.1 Immunogenicity Assessments

The following immunogenicity assessments are planned:

- Serum antibody level as measured by HAI assay for primary, secondary, and exploratory analyses
- NA-specific antibody levels as measured by NAI assay for primary, secondary, and exploratory analyses
- Serum neutralizing antibody level as measured by microneutralization (MN) assay or similar method for secondary or exploratory analysis

- Cellular immunogenicity for exploratory subset analysis. No summary table or listing will be provided.

6.5.2 Primary Analysis of Immunogenicity

GMTs and GMFRs:

For each vaccination group, the following evaluations will be performed at Day 1 (if applicable) and Day 29.

- GMT of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at Day 1 and Day 29, GMT of vaccine-matched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at Day 1 and Day 29, GMFR of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at Day 29 over pre-injection baseline at Day 1.
- GMFR of vaccine-matched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at Day 29 over pre-injection baseline at Day 1.
- In addition, the following descriptive statistics will also be provided at Day 29: the number of participants (n), median, minimum, and maximum.

Seroconversion:

For each vaccination group, the following evaluations will be performed at Day 29.

- For HA, the number and percentage of participants with seroconversion at Day 29 will be provided with 2-sided 95% CI using the Clopper-Pearson method.

For HA, seroconversion is defined as:

1. If LLOQ is 1:10, 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.

2. If LLOQ is greater than 1:10 (e.g. 1:14), a Day 29 titer ≥ 4 times of LLOQ if baseline is < LLOQ or a 4-fold or greater rise if baseline is ≥ LLOQ in anti- HA antibodies measured by HAI assay.

2-/3-/4-fold Rise:

For NA, an endpoint of interest is the percentage of participants with a change in the

Day 29 titer of at least 2-/3-/4-fold rise from baseline.

Definition: 2-/3-/4-fold rise is defined as ≥ 2-/3-/4-fold of the LLOQ if the Day 1 titer is < LLOQ; or ≥ 2-/3-/4-fold of the Day 1 titer if the Day 1 titer ≥ LLOQ.

For each vaccination group, the following evaluations will be performed at Day 29.

- The number and percentage of participants with a ≥ 2-fold rise at Day 29 in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.
- The number and percentage of participants with a ≥ 3-fold rise at Day 29 in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.
- The number and percentage of participants with a ≥ 4-fold rise at Day 29 in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.

6.5.3 Secondary Analysis of Immunogenicity

For each vaccination group, the following evaluations will be performed at all evaluable humoral immunogenicity time points.

GMTs and GMFRs:

- GMT of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each time point,. Geometric mean (GM) level and corresponding 95% CI will be plotted at each time point.
- GMT of vaccine-matched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at each time point.GM level and corresponding 95% CI will be plotted at each time point.
- GMFR of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection baseline at Day 1. GMFR and corresponding 95% CI will be plotted at each time point.
- GMFR of vaccine-matched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection

baseline at Day 1. GMFR and corresponding 95% CI will be plotted at each time point.

- In addition, the following descriptive statistics will also be provided at each time point: the number of participants (n), median, minimum, and maximum.
- Reverse cumulative distribution function curve at each time point will be provided.
- Listing of anti-HA antibodies for vaccine-matched seasonal influenza A and B strains will be provided based on the PP Set.
- Listing of anti-HA antibodies for vaccine-matched seasonal influenza A and B strains for participants with influenza infection will be provided based on the PP Set.
- Listing of anti-NA antibodies for vaccine-matched seasonal influenza A and B strains will be provided based on the PP Set.
- Listing of anti-NA antibodies for vaccine-matched seasonal influenza A and B strains for participants with influenza infection will be provided based on the PP Set.

Seroconversion:

For each vaccination group, the following evaluations will be performed at each post-baseline time point.

- For HA, the number and percentage of participants with seroconversion at each post-baseline time point will be provided with 2-sided 95% CI using the Clopper-Pearson method.

2-/3-/4-fold Rise:

For NA: For each vaccination group, the following evaluations will be performed at each post-baseline time point.

- The number and percentage of participants with a ≥ 2-fold rise at each post-baseline time point in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.

- The number and percentage of participants with a ≥ 3-fold rise at each post-baseline time point in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.
- The number and percentage of participants with a ≥ 4-fold rise at each post-baseline time point in anti-NA antibody titers from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method.

6.5.4 Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- GMT of vaccine-mismatched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each time point using methods described in Section 6.5.
- GMT of vaccine-mismatched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at each time point using methods described in Section 6.5.
- GMFR of vaccine-mismatched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection baseline at Day 1 using methods described in Section 6.5.
- GMFR of vaccine-mismatched strain-specific anti-NA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection baseline at Day 1 using methods described in Section 6.5.
- Summary of RT-PCR results at Baseline.
- Summary of detected influenza results by RT-PCR at post-baseline by time period.
- Listing of anti-HA antibodies for vaccine-mismatched influenza A and B strains will be provided based on the PP Set.
- Listing of anti-HA antibodies for vaccine-mismatched influenza A and B strains for participants with influenza infection will be provided based on the PP Set. Listing of anti-NA antibodies for vaccine-mismatched influenza A and B strains will be provided based on the PP Set.
- Listing of anti-NA antibodies for vaccine-mismatched influenza A and B strains for participants with influenza infection will be provided based on the PP Set.

6.6 Analysis of Influenza Infection

Influenza infection during the study is an exploratory endpoint, and the analyses of influenza infection confirmed by RT-PCR test may be performed using the FAS.

Due to the ongoing COVID-19 pandemic, participants may get infected with SARS-CoV-2 or experience symptoms consistent with influenza-like illness (ILI) during the study.

NP swab samples will be collected from all participants before the injection on Day 1 for assessment of asymptomatic infection with respiratory pathogens, including influenza virus and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessment. Furthermore, if a participant experiences any signs or symptoms suggesting ILI and/or COVID-19, an additional NP swab sample will be collected to confirm the diagnosis via RT-PCR.

A CDC-defined ILI is defined as body temperature ≥ 37.8°C (100°F) accompanied by cough and/or sore throat. An RT-PCR confirmed ILI is defined as a positive influenza result by RT-PCR done at any setting during the study period.

Summaries below will be provided, unless otherwise specified.

- RT-PCR test results at baseline will be summarized by test and vaccination group. Participants with positive influenza results at baseline will be presented in a listing.
- The number and percentage of participants with at least one positive influenza result at post-baseline will be provided by vaccination group. Participants with at least one positive influenza result at post-baseline will be presented in a listing.

6.7 Interim Analysis

One interim analysis (IA) is planned in this study. It will be performed after participants have completed the Day 29 visit.

This interim analysis will be focused on providing insight on the primary study objectives using the available data.

The IA will include safety and immunogenicity and will be performed after participants have completed the Day 29 visit. All data relevant to the IA through the Day 29 visit will be cleaned (i.e., data that are as clean as possible).

A limited number of Sponsor and CRO personnel will be unblinded to perform the IAs. Please refer to the DBP for more details on the blinding of IA.

An independent, unblinded statistics team will carry out the IA. The unblinded statistics team will not be involved in either study design or the regular study conduct. The study site staffs, investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis.

6.8 Internal Safety Team Review

The safety monitoring for this study will include a group of blinded study team members, inclusive of, at a minimum, a Sponsor medical monitor, a CRO medical monitor, a blinded IST, and an unblinded DSMB.

The IST will comprise Sponsor physicians. The IST will conduct a scheduled review of safety data after approximately 96 participants (12 per study arm) have completed the Day 8 visit as well as ad hoc safety data reviews if requested by the study team. Enrollment will continue while these reviews are 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. Details regarding the IST composition, responsibilities, procedures, and frequency of data review will be defined in the mRNA-1020-P101 Internal Safety Team (IST) Charter.

6.9 Data Safety Monitoring Board Review

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 unblinded review of safety data from this study population.

The DSMB will conduct unblinded reviews of safety data on an ad hoc basis if any pause rule is met or as requested by the study team and /or IST.

The DSMB will also review unblinded IA results provided by the independent unblinded statistician.

A secure file transfer path will be decided between the CRO and Sponsor to use for the transfer of unblinded study data for DSMB review. Only the CRO independent unblinded

biostatistician, unblinded programmer(s), unblinded medical monitor (if assigned for unblinded DSMB review), and unblinded Sponsor clinical representative (if assigned for unblinded DSMB review) will have access to upload the unblinded data package to the secured file transfer location to be delivered to the DSMB. Refer to the mRNA-1020-P101 Data Safety Monitoring Board (DSMB) Charter for more details.

6.10 Subgroup Analysis

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform formal subgroup analyses. However, age-specific subgroup analyses may be performed to explore for potential differences in safety/reactogenicity or immune responses across age groups.

7 CHANGES FROM PLANNED ANALYSES IN PROTOCOL

Not applicable.

8 REFERENCES

Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007.

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

9 LIST OF APPENDICES

9.1 *Appendix A Standards for Safety and Immunogenicity Variable Display in TLFs*

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

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

9.2 *Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis*

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

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

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 4 below.

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

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 4 Analysis Visit Window

Visit	Target Study Day	Visit Window in Study Day
Labs		
Day 8	8	[2, 18]
Immunogenicity		
Day 1	1 (Date of Vaccination)	1, Pre-vaccination
Day 8	8	[2, 18]
Day 29	29	[19, 105]
Day 181	181	≥106

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

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

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of injection or is missing AND the start month and year of the medication coincide with the start month and year of the injection. In this case, use the date of injection.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of injection or is missing AND the start year of the medication coincide with the start year of the injection. In this case, use the date of injection
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication end date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant, or post categorization of a medication is described in Table 5 below.

Table 5 Prior, Concomitant, and Post Categorization of Medications and Non-Study Vaccinations

	Medication End Date		
Medication Start Date	**< Injection Date of IP**	**≥ Injection Date and ≤ Injection Date + 27 Days**	**> Injection Date + 27 days [1]**
< Injection date of IP [2]	P	P, C	P, C, A
≥ Injection date and ≤ Injection date + 27 days	-	C	C, A
> Injection date + 27 days	-	-	A

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

9.4 *Appendix A Imputation Rules for Missing AE Dates*

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

1. Missing or partial AE start date:
   - If only Day is missing, use the first day of the month, unless:
     - The AE end date is after the date of the injection or is missing AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date and time of the injection, even if time is collected.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The AE end date is after the date of the injection or is missing AND the start year of the AE coincides with the start year of the injection. In this case, use the date of the injection
   - If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of the injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.
2. Missing or partial AE end dates will not be imputed.

9.5 *Appendix E Severity Grading of Laboratory Abnormalities*

Serum*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - mg/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - mg/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - mg/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – mg/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

9.6 *Appendix F Severity Grading of Vital Sign Abnormalities*

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

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