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ModernaTX, Inc.

Protocol mRNA-1083-P301A Phase 3, randomized, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in healthy adult participants ≥ 50 years of age

Statistical Analysis Plan

SAP Version 2.0

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	05-OCT-2023	Original Version (Version 1.0)
2.0	25-MAR-2024	Section 2.2 and 3.2 updated for the MN assay secondary objective and endpoint Section 4.2 updated for hypotheses contents regarding superiority success criteria Section 6.4 updated for multiplicity control per updated hypotheses testing sequence for coprimary and secondary endpoints Section 5.5 updated for per protocol immunogenicity set and per protocol immunogenicity set (PPIS) for MN assay added Section 6.1 updated treatment arm label and subgroup definition Section 6.2.1 updated with PPIS for MN assay Section 6.2.2 updated with PPIS for MN assay and subgroup language Section 6.2.5 updated with PPIS for MN assay Section 6.3 updated for the MN assay secondary endpoints and Day 181 analysis, 97.5% CI removed from the secondary & exploratory endpoints Section 6.5 updated for injection content and pooled analysis across cohorts, AE leading to treatment discontinuation language removed Appendix H updated with SMQ table Appendix I added for immunogenicity sampling plan

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LIST OF ABREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CEAC	cardiac event adjudication committee
CI	confidence interval
CDC	US Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EoS	end of study
EQ 5D 5 L	EuroQol 5-dimension 5-level
eDiary	electronic diary
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
HAI	hemagglutination inhibition
HCP	healthcare professional
HD	high dose
IA	interim analysis

ILI	influenza-like illness
IM	intramuscular
IP	investigational product
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NA	not applicable
NP	nasopharyngeal
NI	noninferiority
NIM	noninferiority margin
PP	Per-Protocol
PPIS	Per Protocol Immunogenicity Set
PsVNA	pseudovirus neutralization assay
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
SCR	seroconversion rate
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
SoA	schedule of activities
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

WPAI	work productivity and activity impairment

1 INTRODUCTION

This statistical analysis plan (SAP), which describes the planned analyses for study mRNA-1083-P301, is based on the most recent approved clinical study protocol (CSP), dated 22-MAR-2024, and the most recent approved electronic case report form (eCRF), dated 18-OCT-2023.

In addition to the principal features of analyses for this study described in Section 9 of the protocol, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1083-P301 is a phase 3, randomized, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in healthy adult participants ≥ 50 years of age.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, immunogenicity and efficacy 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 primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, study vaccination, intervention administration, injection of investigational product (IP)/ investigational vaccine, dosing, and injection are used interchangeably. Treatment group, investigational treatment arm, treatment arm are used interchangeably.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Cohort A Substudy (≥65 Years)

To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine matched strains for influenza and SARS-CoV-2 at Day 29.

To evaluate the safety and reactogenicity of study injections across treatment arms.

Cohort B Substudy (≥50 to <65 Years)

To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.

To evaluate the safety and reactogenicity of study injections across treatment arms.

2.2 Secondary Objectives

Cohort A Substudy (≥65 Years)

To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.

To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.

To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.

Cohort B Substudy (≥50 to <65 Years)

To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.

To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.

To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.

2.3 Exploratory Objectives

The following exploratory objectives may be performed:

Cohort A Substudy (≥65 Years)

To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.

To evaluate the humoral immune responses to vaccine mismatched strains for influenza and SARS-CoV-2 across treatment arms.

To characterize other health outcomes during the first 7 days after study injections.

Cohort B Substudy (≥50 to <65 Years)

To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.

To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across treatment arms.

To characterize other health outcomes during the first 7 days after study injections.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Cohort A Substudy (≥65 Years)

GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post injection level ≥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 post-injection level ≥4-fold rise if Baseline is ≥ LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

Solicited local and systemic ARs through 7 days after study injection.

Unsolicited AEs through 28 days after study injection.

MAAEs from Day 1 through Day 181 (Month 6) or EoS.

AESIs from Day 1 through Day 181 (Month 6) or EoS.

SAEs from the time of informed consent through Day 181 (Month 6) or EoS.

AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.

Cohort B Substudy (≥50 to <65 Years)

GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post injection level ≥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 post injection level ≥4 fold rise if Baseline is ≥LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

Solicited local and systemic ARs through 7 days after each study injection.

Unsolicited AEs through 28 days after each study injection.

MAAEs from Day 1 through Day 181 (Month 6) or EoS.

AESIs from Day 1 through Day 181 (Month 6) or EoS.

SAEs from the time of informed consent through Day 181 (Month 6) or EoS.

AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.

3.2 Secondary Endpoints

Cohort A Substudy (≥65 Years)

GM level at Day 29 by HAI assay for and by PsVNA for SARS-CoV-2.

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥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 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA

GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza.

Cohort B Substudy (≥50 to <65 Years)

GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post injection level ≥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 post injection level ≥4 fold rise if Baseline is ≥LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza.

3.3 Exploratory Endpoints

The following exploratory endpoints may be performed:

Cohort A Substudy (≥65 Years)

GM level and GMFR at all evaluable time points compared with Day 1 by HAI for vaccine matched strains of and by PsVNA for vaccine matched strains of SARS-CoV-2.

- Influenza: Percentage of participants with seroconversion, as defined in Section 3.1.
- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.1.

GM level and GMFR at all evaluable time points compared with Day 1 by HAI for vaccine mismatched strains of influenza and by PsVNA for vaccine mismatched strains of SARS-CoV-2 .

- Influenza: Percentage of participants with seroconversion, as defined in Section 3.1.

- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.1.

Describe EQ-5D-5L health questionnaire utility score through 7 days after study injection.

Cohort B Substudy (≥50 to <65 Years)

GM level and GMFR at all evaluable time points compared with Day 1 by HAI for vaccine matched strains of influenza and by PsVNA for vaccine matched strains of SARS-CoV-2.

- Influenza: Percentage of participants with seroconversion, as defined in Section 3.1.
- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.1.

GM level and GMFR at all evaluable time points compared with Day 1 by HAI for vaccine mismatched strains of influenza and by PsVNA for vaccine mismatched strains of SARS-CoV-2.

- Influenza: Percentage of participants with seroconversion, as defined in Section 3.1.
- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.1.

Describe EQ-5D-5L health questionnaire utility score daily from Day 1 through 7 days after study injection.

Describe WPAI: GH v2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment through 7 days after study injection.

4 STUDY DESIGN

4.1 Overall Study Design

This study will be a Phase 3, randomized, stratified, observer-blind, active-control study conducted in 2 age-group substudies (Cohort A and Cohort B). This clinical study consists of 2 separate substudies:

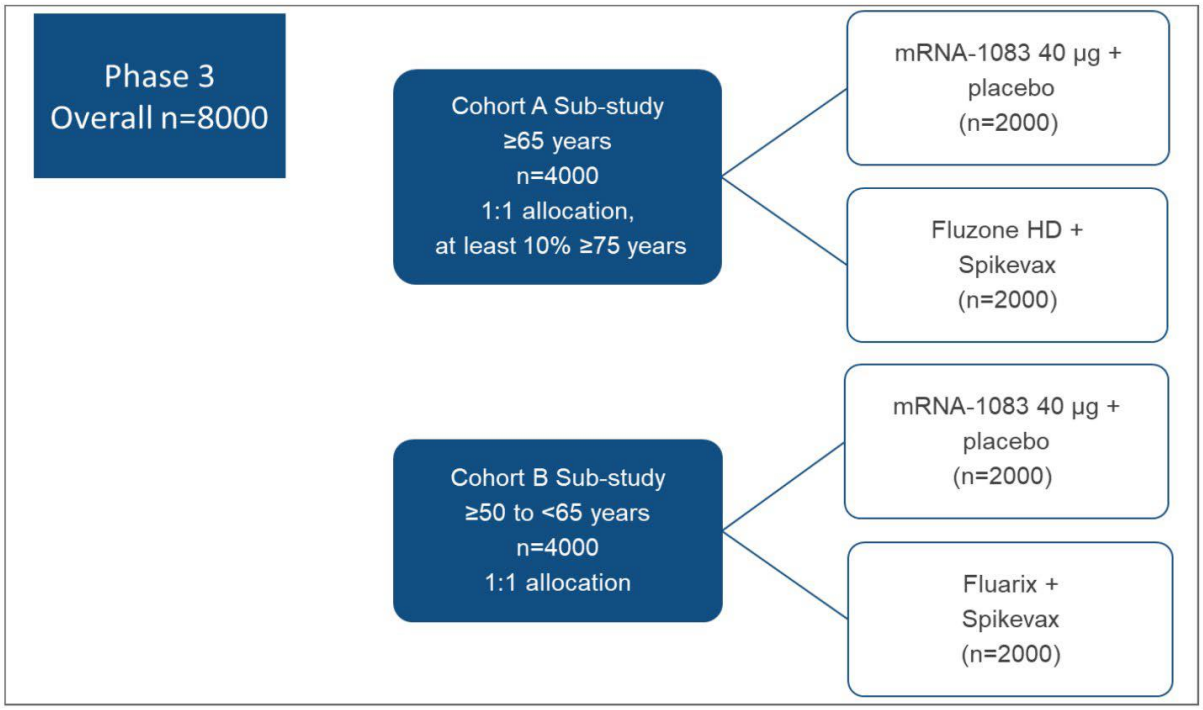
Cohort A will evaluate the safety, reactogenicity, and immunogenicity of the 40 μg mRNA 1083 vaccine and dose level as compared with co administered active licensed comparator vaccines (Fluzone® HD and Spikevax) in healthy adults ≥65 years of age.

Cohort B will evaluate the safety, reactogenicity, and immunogenicity of the 40 μg mRNA 1083 vaccine and dose level as compared with co administered active licensed comparator vaccines (Fluarix® and Spikevax) in healthy adults 50 to <65 years of age.

Each of the 2 independent substudies has its own separate hypotheses and statistical analyses, and its own multiplicity control for overall Type I error rate (2-sided alpha of 5%) for the co-primary endpoints within the substudy.

Overall, the study will enroll approximately 8000 participants with approximately 4000 participants (in a 1:1 ratio) in Cohort A and approximately 4000 participants (in a 1:1 ratio) in Cohort B. The study schema is presented in Figure 1.

Figure 1 Study Schematic and Participant Disposition



On Day 1, each participant will receive 2 injections administered IM, 1 in each deltoid. The interventions administrated are described in Table 1.

Table 1 Study Arms and Interventions Administered

Substudies	Arm Titles	Arm Types	Arm Descriptions
Cohort A (≥65 years of age) n=4000	mRNA 1083 + Placebo n=2000	Experimental	Participants will receive mRNA 1083 (40 µg) and Placebo, administered as IM injections, 1 in each deltoid muscle on Day 1.
	Fluzone HD + Spikevax n=2000	Active Comparator	Participants will receive Fluzone HD and Spikevax administered as IM injections, 1 in each deltoid muscle on Day 1.
Cohort B (50 to <65 years of age) n=4000	mRNA-1083 + Placebo n=2000	Experimental	Participants will receive mRNA-1083 (40 µg) and Placebo, administered as IM injections, 1 in each deltoid muscle on Day 1.
	Fluarix + Spikevax n=2000	Active Comparator	Participants will receive Fluarix and Spikevax, administered as IM injections, 1 in each deltoid muscle on Day 1.

Study details include:

Study duration: approximately 6 months, including the Screening period.

Treatment duration: Study injections are scheduled for all participants on Day 1 (Baseline).

Visit frequency:

- All participants will have scheduled in person clinic visits for Screening and on Day 1 (Baseline) and Day 29 (Month 1).
- All participants will have a safety follow up call on Days 8 and 91 (Month 3).
- On Day 181 (Month 6), at least 800 participants per substudy cohort will have an in-person clinic visit for sample collection. All remaining participants will have a safety follow up call.

For a more detailed presentation of the study, please refer to the Schedule of Activities (SoA) available in Appendix A.

4.2 Statistical Hypotheses

Each of the 2 independent substudies, Cohort A (65 years or greater) and Cohort B (50 to <65 years of age), has its own separate hypotheses and statistical analyses, and its own multiplicity control for overall Type I error rate (2-sided alpha of 5%) for the co-primary endpoints within the substudy. Each of the 2 substudies has the co-primary immunogenicity endpoints as described below.

4.2.1 Hypotheses in Cohort A Substudy (≥65 Years)

There are six statistical hypotheses for the substudy that will be tested sequentially according to the procedures described below:

4.2.1.1 Co-primary Hypotheses

Each of the primary immunogenicity endpoints will be evaluated for noninferiority of mRNA-1083 (40 μg) + Placebo versus Fluzone HD + Spikevax at a 2-sided alpha of 0.025 level for Cohort A for adults aged 65 years or greater. The first two null hypotheses H^1_0 and H^2_0 will be tested simultaneously, as below.

The success criteria of noninferiority on the five co-primary endpoints for GM level are met if H^1_0 is rejected at two-sided 0.025 level. Similarly, the success criteria of noninferiority on the five co-primary endpoints for SCR or SRR are met if H^2_0 is rejected at two-sided 0.025 level.

Five Co-primary Endpoints Based on Influenza and SARS-CoV-2 GM level at Day 29

The null hypothesis H^1_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and 1 SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza and PsVNA for SARS-CoV-2, is inferior compared with that in participants who received Fluzone HD + Spikevax.

The NI in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared with that of participants who received Fluzone HD + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a

NIM of 1.5. The GMR is defined as the ratio of the GM level of HAI or PsVNA in those participants receiving mRNA-1083 (40 μg) + Placebo versus the GM level of those participants receiving Fluzone HD + Spikevax.

Five Co-primary Endpoints Based on Influenza SCR or SARS CoV-2 SRR at Day 29

The null hypothesis H^2_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response in participants who received mRNA-1083 (40 μg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) or SRR using PsVNA (for SARS-CoV-2), is inferior compared with that in participants who received Licensed Fluzone HD + Spikevax.

The NI in SCR or SRR in participants who received mRNA-1083 (40 μg) + Placebo compared with that of participants who received Fluzone HD + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the SCR or SRR difference at Day 29 ruling out -10% (lower bound >-10%) using a NIM of 10%.

For influenza, the SCR at Day 29 is defined as the proportion of participants with either a preinjection HAI level <1:10 and a postinjection HAI level ≥1:40, or a preinjection HAI level ≥1:10 and a minimum 4-fold rise in postinjection HAI antibody level. The SCR difference Day 29 is defined as the difference between the SCR at Day 29 among those participants receiving mRNA-1083 (40 μg) + Placebo and the SCR at Day 29 among those participants receiving Fluzone HD + Spikevax.

For SARS-CoV-2, the SRR at Day 29 is defined as the proportion of participants with either GMFR in nAb levels of ≥4-fold postinjection compared with Day 1 in those with Baseline level ≥LLOQ, or postinjection level ≥4×LLOQ if Baseline level is <LLOQ. The SRR difference at Day 29 is defined as the difference between the SRR at Day 29 among those participants receiving mRNA-1083 (40 μg) + Placebo and the SRR at Day 29 among those participants receiving Fluzone HD + Spikevax.

4.2.1.2 Secondary Hypotheses

If the noninferiority success criteria of the coprimary endpoints for GM level are met, the following hypotheses will be tested sequentially to support secondary objectives:

The null hypothesis H^3_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response as measured using the GM level at Day 29 for the HAI assay for influenza, of mRNA-1083 (40 μg) + Placebo to Fluzone HD + Spikevax is not superior to Fluzone HD + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1) for all 4 influenza strains. It will be tested at a two-sided α_1=5% level if noninferiority is demonstrated for GM level (H^1_0 rejected) and SCR or SRR (H^2_0 rejected); and at a two-sided α_1=2.5% level if non-inferiority is only demonstrated for GM level (H^1_0 rejected).

If the superiority success criteria for GM levels at Day 29 using HAI assay for influenza are met (H^3_0 rejected), the null hypothesis H^4_0 will be tested: for the SARS-CoV-2 strain (Omicron

XBB.1.5), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by GM level at Day 29 using PsVNA is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator, will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1). The same level α_1 will be passed to test hypothesis H^4_0.

If the superiority success criteria for GM levels at Day 29 using PsVNA assay for SARS-CoV-2 are met (H^4_0 rejected), and noninferiority success criteria for SCR or SRR are met (H^2_0 rejected), the hypothesis H^5_0 will be tested. The null hypothesis H^5_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by D29 SCR using HAI assay (for influenza strains), is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in SCR in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SCR difference ruling out 0% (lower bound >0%) for all 4 influenza strains.

If the superiority success criteria for SCR at Day 29 using HAI assay for influenza are met (H^5_0 rejected), the hypothesis H^6_0 will be tested. The null hypothesis H^6_0: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by Day 29 SRR using PsVNA (for SARS-CoV-2) is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in SRR in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SRR difference ruling out 0% (lower bound >0%).

4.2.2 Hypotheses in Cohort B Substudy (≥50 to <65 Years)

There are six statistical hypotheses for the substudy that will be tested according to the procedures described below:

4.2.2.1 Co-primary Hypotheses

Each of the primary immunogenicity endpoints will be evaluated for noninferiority of mRNA-1083 (40 μg) + Placebo versus Fluarix + Spikevax at a 2-sided alpha of 0.025 level for Cohort B for adults aged ≥50 to <65 years. The first two null hypotheses H^1_0 and H^2_0 will be tested simultaneously, as below.

The success criteria of noninferiority on the five co-primary endpoints for GM level are met if H^1_0 is rejected at two-sided 0.025 level. Similarly, the success criteria of noninferiority on the five co-primary endpoints for SCR or SRR are met if H^2_0 is rejected at two-sided 0.025 level.

Five Co-primary Endpoints Based on Influenza and SARS-CoV-2 GM Level at Day 29

The null hypothesis H^1_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and 1 SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response in participants who received mRNA-1083 (40 μg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza and PsVNA for SARS-CoV-2, is inferior compared with that in participants who received Fluarix + Spikevax.

The NI in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared with that of participants who received Fluarix + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a NIM of 1.5. The GMR is defined as the ratio of the GM level of HAI or PsVNA in those participants receiving mRNA-1083 (40 μg) + Placebo versus the GM level of those receiving Fluarix + Spikevax.

Five Co-primary Endpoints Based on Influenza SCR or SARS CoV-2 SRR at Day 29

The null hypothesis H^2_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response in participants who received mRNA-1083 (40 μg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) or SRR using PsVNA (for SARS-CoV-2), is inferior compared with that in participants who received Fluarix + Spikevax.

The NI in SCR or SRR in those participants who received mRNA-1083 (40 μg) + Placebo compared with that of those who received Fluarix + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the SCR or SRR difference at Day 29 ruling out -10% (lower bound >-10%) using a NIM of 10%.

For influenza, the SCR at Day 29 is defined as the proportion of participants with either a preinjection HAI level <1:10 and a postinjection HAI level ≥1:40, or a preinjection HAI level ≥1:10 and a minimum 4-fold rise in postinjection HAI antibody level. The SCR difference Day 29 is defined as the difference between the SCR at Day 29 among those participants receiving mRNA-1083 (40 μg) + Placebo and the SCR at Day 29 among those receiving Fluarix + Spikevax.

For SARS-CoV-2, the SRR at Day 29 is defined as the proportion of participants with either a GMFR in nAb levels of ≥4-fold postinjection compared with Day 1 in those with Baseline level ≥LLOQ or postinjection level ≥4×LLOQ if Baseline level is <LLOQ. The SRR difference at Day 29 is defined as the difference between the SRR at Day 29 among those participants receiving mRNA-1083 (40 μg) + Placebo and the SRR at Day 29 among those receiving Fluarix + Spikevax.

4.2.2.2 Secondary Hypotheses

If the noninferiority success criteria of the coprimary endpoints for GM level are met, the following hypotheses will be tested sequentially to support secondary objectives:

The null hypothesis H^3_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response as measured using the GM level at Day 29 for the HAI assay for influenza, of mRNA-1083 (40 μg) + Placebo to Fluarix + Spikevax is not superior to Fluarix + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1) for all 4 influenza strains. It will be tested at a two-sided α_1=5% level if noninferiority is demonstrated for GM level (H^1_0 rejected) and SCR or SRR (H^2_0 rejected); and at a two-sided α_1=2.5% level if non-inferiority is only demonstrated for GM level (H^1_0 rejected).

If the superiority success criteria for GM levels at Day 29 using HAI assay for influenza are met (H^3_0 rejected), the null hypothesis H^4_0 will be tested: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by GM level at Day 29 using PsVNA is not superior to that in participants who received Fluarix + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1). The same level α_1 will be passed to test hypothesis H^4_0.

If the superiority success criteria for GM levels at Day 29 using PsVNA assay for SARS-CoV-2 are met (H^4_0 rejected), and noninferiority success criteria for SCR or SRR are met (H^2_0 rejected), the hypothesis H^5_0 will be tested. The null hypothesis H^5_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains), is not superior to that in participants who received Fluarix HD + Spikevax. The superiority in SCR in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SCR ruling out 0% (lower bound >0%) for all the 4 influenza strains.

If the superiority success criteria for SCR at Day 29 using HAI assay for influenza are met (H^5_0 rejected), the hypothesis H^6_0 will be tested. The null hypothesis H^6_0: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 μg) + Placebo, as measured by Day 29 SRR using PsVNA (for SARS-CoV-2) is not superior to that in participants who received Fluarix + Spikevax. The superiority in SRR in participants who received mRNA-1083 (40 μg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SRR difference ruling out 0% (lower bound >0%).

4.3 Sample Size and Power

With approximately 2000 participants in Cohort A and 2000 participants in Cohort B (a total of 4000) exposed to study vaccine in the mRNA-1083 (40 μg) + Placebo group, this study will have approximately over 95% probability to observe at least 1 participant with an AE given a true 0.1% AE rate.

A subset of participants will be randomly selected from the FAS of Cohort A and B, respectively, to be tested by microneutralization assay according to the secondary objective.

4.3.1 Cohort A Substudy (≥65 Years)

Immunogenicity results from the participants in Cohort A, will contribute to the primary immunogenicity analyses for Cohort A. With approximately 2000 participants (including the assumed approximate 15% drop-outs) receiving mRNA-1083 (40 μg) + Placebo, and 2000 receiving Fluzone HD + Spikevax, this will provide at least 95% overall power to demonstrate NI across the five co-primary immunogenicity endpoints for GM level at Day 29 between mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately

15% drop-out rate, true GMR of 0.85 (SD of antibody level in natural logarithm being 1.5) and a NIM of 1.5 for GMR in all the 4 influenza strains and 1 SARS-CoV-2 strain.

The study has at least 95% overall power to demonstrate NI across the five co-primary immunogenicity endpoints for SCR or SRR between mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop-out rate, an underlying SRR or SCR of 68% in the mRNA-1083 (40 μg) + Placebo group and an SRR or SCR of 70% in Fluzone HD + Spikevax group (with a true SRR or SCR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza A strains and 1 SARS-CoV-2 strain, and assumes an underlying SCR of 58% in the mRNA-1083 (40 μg) + Placebo group and a SCR of 60% in Fluzone HD + Spikevax group (with a true SCR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza B strains.

4.3.2 Cohort B Substudy (≥50 to <65 Years)

Immunogenicity results from the participants in Cohort B will contribute to the primary immunogenicity analyses for Cohort B. With approximately 2000 participants (including the assumed approximate 15% drop-outs) receiving mRNA-1083 (40 μg) + Placebo, and 2000 receiving Fluarix + Spikevax, this will provide at least 95% overall power to demonstrate NI across the five co primary immunogenicity endpoints for GM level at Day 29 between mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax in all the 4 influenza strains and 1 SARS CoV 2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop out rate, true GMR of 0.85 (SD of antibody level in natural logarithm being 1.5) and a NIM of 1.5 for GMR in all the 4 influenza strains and 1 SARS CoV 2 strain.

The study has at least 95% overall power to demonstrate NI across the five co-primary immunogenicity endpoints for SCR or SRR between mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop-out rate, an underlying SRR or SCR of 68% in the mRNA-1083 (40 μg) + Placebo group and an SRR or SCR of 70% in Fluarix + Spikevax group (with a true SRR or SCR difference being 2%) and a NIM of 10% for the rate difference in the 2 influenza A strains and 1 SARS CoV 2 strain, and assumes an underlying SCR of 58% in the mRNA 1083 (40 μg) + Placebo group and a SCR of 60% in Fluarix + Spikevax group (with a true SCR difference being 2%) and a NIM of 10% for the rate difference in the 2 influenza B strains.

4.4 Randomization

Randomization will be performed using an interactive response technology (IRT) by a 3rd party vendor.

Cohort A Substudy (≥65 Years)

In Cohort A randomization (in a 1:1 ratio) will be stratified by age groups (65 to <75 years and ≥75 years of age where at least 10% of participants are ≥75 years of age) and the influenza vaccine status in the most recent influenza season (received or not received since September 2022).

Cohort B Substudy (≥50 to <65 Years)

In Cohort B randomization (in a 1:1 ratio) will be stratified by the influenza vaccine status in the most recent influenza season (received or not received since September 2022).

4.5 Blinding and Unblinding

This is an observer-blind study. An independent unblinded statistical and programming team will perform the preplanned primary analysis (see Section 4.5). Sponsor team members will be prespecified to be unblinded to the primary analysis and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants.

The planned analyses are described in Section 6.7 of this SAP. For further details on preidentified sponsor and CRO team members (identified by role), and the level of unblinding (treatment arm level unblinding and/or participant level unblinding) please refer to the study Data Blinding Plan.

5 ANALYSIS SETS

Each of Cohort A and Cohort B substudies will have its separate set of analysis populations defined as below that will be applied in separate statistical analyses planned in each of the 2 cohorts, respectively.

5.1 Randomization Set

The randomization set consists of all participants who are randomly assigned. Participants will be included in the treatment arm to which they are randomized.

5.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all participants who are randomly assigned and receive the study intervention. Participants will be analyzed according to the treatment arm to which they were randomized.

5.3 Immunogenicity Set

All participants in the FAS who have baseline and Day 29 antibody assessment via HAI or PsVNA assay. Participants will be analyzed according to the treatment arm to which they were randomized.

5.4 Per Protocol Immunogenicity Set

The Per Protocol Immunogenicity Set (PPIS) will be used as the primary analysis set for analyses of immunogenicity in Cohort A or Cohort B unless otherwise specified. Participants will be analyzed according to the treatment arm to which they were randomized.

The PPIS consists of all the participants in the FAS who comply with the timing of immunogenicity blood sample collections to have both Baseline (see Section 6.1) and Day 29 assessments using a window of -7 to +14 days, have no major dosing error, have negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and have no major protocol deviations or conditions/medications that affect the immune response.

The major dosing error ranges, available in Table 2, will be used to determine participant exclusion from the PPIS analysis populations.

5.5 Per Protocol Immunogenicity Set for MN assay

The PPIS for MN assay will be used as the secondary analysis set for analyses of immunogenicity in Cohort A or Cohort B for influenza unless otherwise specified. Participants will be analyzed according to the treatment arm to which they were randomized.

The Per Protocol Immunogenicity Set for MN assay consists of a subset of participants randomly sampled from the Full Analysis Set to be tested for MN, who comply with the timing of immunogenicity blood sampling collections to have both Baseline (see section 6.1) and Day 29 assessments using a window of -7 to +14 days, have no major dosing error, have negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and have no major protocol deviations or conditions/medications that affect the immune response.

The major dosing error ranges, available in Table 2, will be used to determine participant exclusion from the PPIS for MN assay analysis populations.

Table 2 Exclusion Condition for Dosing Errors

Substudies	Arm Titles	Exclusion Conditions
Cohort A (≥65 years of age)	mRNA 1083 + Placebo	Any of the following received: mRNA-1083 ≤ 30 µg OR mRNA-1083 > 60 µg OR Fluarix OR Fluzone HD OR Spikevax
	Fluzone HD + Spikevax	Any of the following received: Fluzone HD ≤180 µg OR Spikevax ≤37.5 µg OR mRNA-1083 OR Fluarix
Cohort B (50 to <65 years of age)	mRNA 1083 + Placebo	Any of the following received: mRNA-1083 ≤ 30 µg OR mRNA-1083 > 60 µg OR Fluarix OR Fluzone HD OR Spikevax
	Fluarix + Spikevax	Any of the following received: Fluarix ≤45 µg OR Spikevax ≤37.5 µg OR mRNA-1083 OR Fluzone HD

5.6 Safety Set

The Safety Set consists of all participants who are randomly assigned and receive the study intervention. The Safety Set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the treatment arm corresponding to what they actually received according to the as treated scheme given below in Table 3.

Table 3 Inclusion Conditions for Safety Set

Substudies	Arm Titles	Inclusion Conditions
Cohort A (≥65 years of age)	mRNA 1083 + Placebo	Any mRNA 1083 dose
	Fluzone HD + Spikevax	Any Fluzone HD dose OR Any Fluarix dose OR Any Spikevax dose
Cohort B (50 to <65 years of age)	mRNA 1083 + Placebo	Any mRNA 1083 dose
	Fluarix + Spikevax	Any Fluarix dose OR Any Fluzone HD dose OR Any Spikevax dose

5.7 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 treatment arm corresponding to what they actually received.

6 STATISTICAL ANALYSIS

6.1 General Considerations

All analyses will be conducted using SAS Version 9.4 or higher. Statistical outputs (tables, figures, listings, and datasets) will refer study participants as participants and will use injection of IP and injection interchangeably.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, Q1 and Q3 (only for summaries specified below), as well as minimum (min), and maximum (max). For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please refer to Appendix B.

Summaries that require Q1 and Q3 for descriptive statistics:

Demographic and baseline characteristics

Study duration

Characteristics of solicited adverse reactions within 7 days after injection

Descriptive summaries of antibody levels

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

Baseline value, unless specified otherwise, is defined as the most recent non missing measurement (scheduled or unscheduled) collected before the dose/time of IP in this study.

For immunogenicity tests and nasal swab tests, the baseline is defined as the most recent non missing result/measurement (scheduled or unscheduled) collected before or on the date of injection (Day 1). If there are multiple valid results on the same 1st injection date/time or date (if time is not available) the largest value will be considered in the immunogenicity baseline derivation.

The following analysis periods of safety analyses will be used:

Within 7 days after injection, this period includes the day of vaccination and 6 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period will be used for unsolicited and solicited local and systemic AR that occur during this time.

Up to 28 days after injection, starts from the day of vaccination (Day 1) and spans 28 days to include the day of vaccination and 27 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

Throughout the Study, from the day of vaccination (Day 1) and continues through the earliest date of (study completion, discontinuation from the study, or death).

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

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

In scheduled visit windows per specified visit windowing rules (Appendix C).

In the derivation of baseline/last on-treatment measurements.

In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.

In individual participant data listings.

Age: unless otherwise specified, age is calculated as the age at screening. In the analyses for subgroups defined by age, age at screening will be used for derivation of age groups.

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

study day prior to the injection will be calculated as: date of assessment/event – date of the injection (resulting in negative study day);

study day on or after the date of the injection will be calculated as: date of assessment/event – date of the injection + 1;

Duration of an event will be calculated as (Event end date – Event start date +1). The duration of the study will be calculated for the participants included in the safety set:

Since randomization: date of last visit (as recorded on End of Study [EoS] eCRF) – date of randomization + 1,

Since study injection: date of last visit (as recorded on End of Study [EoS] eCRF) – date of injection + 1.

If the last visit date on the EoS eCRF page is missing, then the latest of either the cut-off date or the last available visit date will be employed. The durations of solicited ARs will be calculated as: reaction end date – reaction start date +1, regardless of whether the AR is intermittent or continued or if the solicited AR continues beyond 7 days.

Incomplete/missing data: Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix D. Imputation rules for missing AE dates are provided in Appendix E. Other incomplete/missing data will not be imputed, unless specified otherwise.

For calculation regarding antibody levels/titers,

values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ,

values reported as above the upper limit of quantification (ULOQ) will be converted to the ULOQ,

Missing results will not be imputed.

Treatment arm will be presented according to the analysis set of interest, unless otherwise specified. All the statistical analyses will be performed and presented for Cohort A and Cohort B separately. The following treatment arm labels will be used for summary purposes for Cohort A and for Cohort B tables and figures outputs, respectively:

Cohort A Substudy (≥65 Years)

mRNA 1083 40 µg + Placebo

Fluzone HD + Spikevax

Overall (All treatment arms combined; details are available below)

Cohort B Substudy (≥50 to <65 Years)

mRNA 1083 40 µg + Placebo

Fluarix + Spikevax

Overall (All treatment arms combined; details are available below)

The "Overall" combined group will be presented for the summaries of disposition, major protocol deviation, medical history, concomitant medication and baseline demographic only.

Table layouts: Tables and figures will be outputted for all the participants. Where indicated in this SAP, the following subgroups, detailed in Table 4, will be used for summary purposes. Unless otherwise specified, all subgroups are based on eCRF.

Table 4 Subgroups Definition

Substudies	Subgroup Variables	Categories
Cohort A (≥65 years of age)	Age Group	65 to <75 years ≥75 years
	Influenza vaccine status since Sept 2022 (only for immunogenicity analyses)	Received previous season flu vaccine Did not receive previous season flu vaccine
	Covid vaccine status since September 2022 (only for SARS-CoV-2 related immunogenicity analyses)	Received previous Covid vaccine Did not receive previous Covid vaccine
	Number of prior covid vaccines (only for SARS-CoV-2 related immunogenicity analyses)	No Dose, 1 - 2 Doses, 3 Doses, 4 Doses, >=5 Doses
	Baseline SAS-CoV-2 Infection Status (only for SARS-CoV-2 related immunogenicity analyses)	Positive, Negative
	Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
	Ethnicity	Hispanic or Latino Not Hispanic or Latino
	Sex	Male Female
	BMI	< 30 kg/m^2 ≥ 30 kg/m^2
Cohort B (50 to <65 years of age)	Influenza vaccine status since Sept 2022 (only for immunogenicity analyses)	Received previous season flu vaccine Did not receive previous season flu vaccine
	Covid vaccine status since September 2022 (only for SARS CoV 2 related immunogenicity analyses)	Received previous Covid vaccine Did not receive previous Covid vaccine

	Number of prior covid vaccines (only for SARS CoV 2 related immunogenicity analyses)	No Dose, 1 - 2 Doses, 3 Doses, 4 Doses, >=5 Doses
	Baseline SAS-CoV-2 Infection Status (only for SARS-CoV-2 related immunogenicity analyses)	Positive, Negative
	Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
	Ethnicity	Hispanic or Latino Not Hispanic or Latino
	Sex	Male Female
	BMI	< 30 kg/m^2 ≥ 30 kg/m^2

6.2 Background Characteristics

6.2.1 Participant Disposition

The number and percentage of participants in each of the following disposition categories will be summarized by treatment arm (as defined in Section 6.1) based on the Randomization Set, Safety Set, and PP Immunogenicity Set (as defined in Section 5):

Received study injection

Completed the study

Prematurely discontinued the study and the reason for discontinuation

This study treatment consists of 2 injections administered IM, thus discontinuation from study treatment is applicable if a participant receives only 1 of the 2 planned injections. A Participant is considered to have completed the study if he or she has completed the study including the last Day 181 scheduled procedure (SoA).

Participant randomization and disposition listings will be provided, including randomization information such as randomization date, number, planned and actual treatment arm and stratification used, informed consent, participants who received study injection, participants who completed study, participants who discontinued from study, with reasons for discontinuation. In

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

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

Number of participants screened

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

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

A screen failure listing will be provided including information on the screen failed participants and the reasons for screen failure.

The number and percentage of participants randomized with respect to each combined stratification factor at randomization by IRT will be summarized by treatment arm (as defined in Section 6.1) based on the Randomization Set:

Cohort A Substudy (≥65 Years)

≥65 to <75 years and Received an influenza vaccine since September 2022,

≥65 to <75 years and Did Not Receive an influenza vaccine since September 2022,

≥75 years and Received an influenza vaccine since September 2022,

≥75 years and Did Not Receive an influenza vaccine since September 2022,

Cohort B Substudy (≥50 to <65 Years)

Received an influenza vaccine since September 2022,

Did Not Receive an influenza vaccine since September 2022,

If IRT and eCRF stratum are not concordant, then a concordance table will be presented, by treatment arm (as defined in Section 6.1) based on the Randomization Set, with the number and percentage of patients in IRT randomization stratum and actual stratum derived from eCRF.

The number and percentage of participants in the following Analysis Sets (see Section 5) will be summarized by treatment arm (as defined in Section 6.1) based on the Randomization Set:

Randomization Set,

Full Analysis Set,

Immunogenicity Set,

Per Protocol Immunogenicity Set,

Per Protocol Immunogenicity Set for MN Assay,

Safety Set,

Solicited Safety Set.

For Solicited Safety Set, the percentage will be based on the number of participants in the treatment arm within the Safety Set (as treated). A summary of reasons for participants excluded from the Per Protocol Immunogenicity Set will also be provided.

A listing, including information related to the different Analysis Sets of the randomized participants as well as the reason for exclusion from analysis set will be added.

6.2.2 Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics:

Age (years)

Weight (kg)

Height (cm)

Body mass index (kg/m2)

The number and percentage of participants will be provided for the following categorical variables:

Age group (≥65 to <75 years old, ≥75 years for Cohort A, ≥ 50 to < 65 years old for Cohort B, separately) per age reported on the eCRF

BMI group (< 30 kg/m2, ≥30 kg/m2)

Sex (Male, Female)

Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Other, Unknown, Not Reported)

Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

Frailty Status for participants ≥65 years of age (Edmonton Frail Scale total score 0-3: Fit, 4-5: Vulnerable, 6 or more: Frail)

Influenza vaccine status in the most recent influenza season (received or not received since Sept 2022) per eCRF

Covid vaccine status since September 2022 (received or not received)

Number of Covid vaccinations (No Dose, 1-2 Doses, 3 Doses, 4 Doses, >=5 Doses)

Childbearing Potential for female participants (Yes/No) and reason if "No"

Baseline SARS-CoV-2 RT-PCR Results (positive, negative, or missing)

Baseline Elecsys Anti-SARS-CoV-2 Results (positive, negative, or missing)

Baseline SARS-CoV-2 Status (positive, negative, or missing)

Baseline Influenza Infectious Status (positive, negative, or missing)

The summaries will be provided separately for all analysis sets (except for Immunogenicity Set and Solicited Safety Set) defined in the Section 5, by treatment arm (as defined in Section 6.1).

Demographic and baseline characteristics will be provided listings for randomized and screened failed participants. The number and percentage of participants randomized by country and site will be provided as well.

6.2.3 Medical History

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

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set, by treatment arm (as defined in Section 6.1). A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the "1083 + Placebo" group and then alphabetically within SOC. Medical history data will be presented in a listing.

6.2.4 Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications and imputation rules for missing/partial dates is summarized in Appendix D.

An overall summary with the number and percentage of participants using concomitant medications and non-study vaccination that continued or newly received at or after the injection, 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 provided by treatment arm (as defined in Section 6.1) as follows:

Any concomitant medications and non-study vaccination within 7 days postinjection

Any concomitant medications and non-study vaccination within 28 days postinjection

Any seasonal influenza or COVID-19 Vaccine within 28 days postinjection

An additional summary table of concomitant medications and non-study vaccination that continued or newly received at or after the injection through 28 days will be provided by PT in descending frequency based on "1083 + Placebo" group.

Medications taken to prevent or treat pain or fever will be collected in the electronic diary (eDiary). A summary table will be provided based on the Solicited Safety Set by treatment arm (as defined in Section 6.1), including within 7 days after injection.

Prior and concomitant medications and non-study vaccination will be presented in a listing. Medications taken to prevent or treat pain or fever will be presented as well (see Section 6.5.1.1 on solicited ARs listings).

Concomitant Procedures will be presented in a listing.

6.2.5 Protocol Deviations

The noncompliance may be either on the part of the participant, the Investigator, or the study site staff (or delegate). As a result of deviations, corrective actions are to be developed by the site

and implemented promptly. Major protocol deviations are a subset of protocol deviations that may affects primary efficacy and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial project. 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 treatment arm (as defined in Section 6.1), based on the Randomization Set.

Selected major protocol deviations might impact critical or key study data such as the immune response. Participants with such deviations will be excluded from the PPIS and PPIS for MN assay. Such major protocol deviations will be determined and documented by Sponsor prior to database lock and unblinding. Reasons of exclusion from the PPIS set will be summarized. Major protocol deviations will be presented in a listing.

6.2.6 Study Exposure

Study duration (the study duration calculation is available in Section 6.1) will be summarized by treatment arm (as defined in Section 6.1) since randomization, and since the study injection based on Safety Set. Study vaccine administration data will be presented in a listing. Participants with any dosing errors will also be presented in a separate listing.

6.2.7 COVID-19 Impact

A listing will be provided for COVID-19 impact on missed or out of window visits or assessments for participants in Safety Set.

6.3 Immunogenicity Analyses

The primary analysis population for immunogenicity will be the Per Protocol Immunogenicity Set, unless otherwise specified. A subset of participants will be randomly selected from the FAS of cohort A and B, respectively, to be tested by MN assay for the secondary objective. The sampling method and process to obtain the subset are described in Appendix I. The analysis population for this immunogenicity subset will be the Per Protocol Immunogenicity Set for MN Assay, unless otherwise specified. Some of the further immunogenicity analyses may be performed in a subset of participants.

For humoral immunogenicity (except for MN assay) on Day 1 and Day 29, samples will be collected and analyzed for all participants of each cohort. For Day 181, samples will be collected and analyzed for the first 800 participants of each cohort. Plasma and serum from humoral immunogenicity samples will be stored for potential future use.

The following analytes will be measured:

Influenza: Serum antibody level as measured by HAI assay and serum nAb level as measured by microneutralization assay.

SARS-CoV-2: Serum nAb levels as measured by PsVNA assay by enzyme linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.

Please refer to Appendix C for details regarding the analysis visit window or in case of multiple postbaseline assessment available.

For the primary, secondary, and exploratory endpoints, the GM level (GMT) will be calculated using the following formula (Nauta, 2011):

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

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

The 95% CIs for GM level 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.

6.3.1 Primary Immunogenicity Endpoints Analysis

For each substudy, there is a total of five co-primary endpoints based on GM level, and five co-primary endpoints based on seroconversion and seroresponse for the vaccine-matched strains. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants receiving mRNA-1083.

6.3.1.1 Cohort A Substudy (≥65 Years): Primary Analyses

The primary objective of Cohort A is to evaluate the immunogenicity response between the participants receiving mRNA-1083 (40 μg) + Placebo and those receiving Fluzone HD + Spikevax among the adults ≥65 years of age. Immune responses for influenza, as measured by GM level and SCR at Day 29 by HAI assay in the group of mRNA-1083 (40 μg) + Placebo, will be compared with those in the participants receiving Fluzone HD + Spikevax for all 4 influenza strains. Immune responses for SARS-CoV-2, as measured by GM level and SRR at Day 29 by PsVNA in the group of mRNA-1083 (40 μg) + Placebo, will be compared with those participants receiving Fluzone HD + Spikevax for the matched strain.

Five Co-primary Endpoints Based on Influenza and SARS-CoV-2 GM level at Day 29

An ANCOVA model will be carried out including the log-transformed HAI or PsVNA levels at Day 29 as the dependent variable, the treatment group as the fixed variable and log transformed baseline HAI or PsVNA levels as a fixed covariate. The model will be adjusted for the stratification factors (age group: 65 to <75 years of age and 75 years of age or greater and the influenza vaccine status in the most recent influenza season: received or not received since September 2022).

The GM level will be estimated by the geometric least square mean (GLSM) from the ANCOVA model for each treatment arm and corresponding 2-sided 95% CI will be provided. The GLSM and its corresponding CI in log-transformed scale will be back-transformed to the original scale to obtain an estimate of the GM level.

GMR will be estimated by the ratio of GLSM and the corresponding 2-sided 95% and 97.5% CI to assess the immune response difference between the group of mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax and presented by treatment arm (as defined in Section 6.1).

For each strain of influenza and SARS-CoV-2, the NI of GM level will be considered demonstrated between the group of mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax if the lower bound of the 97.5% CI of the GMR is >0.667 based on the prespecified NIM of 1.5.

GM level and GMR at Day 29 will be plotted.

Five Co-primary Endpoints Based on Influenza SCR and SARS-CoV-2 SRR at Day 29

Seroconversion and seroresponse are defined as follow:

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥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 post-injection level ≥4-fold rise if Baseline is ≥ LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

The number and percentage of participants with either seroconversion (for influenza) or seroresponse (for SARS-CoV-2) postvaccination at Day 29 will be provided along with the two-sided 95% CI of SCR or SRR estimated using the Clopper-Pearson method and presented by treatment arm (as defined in Section 6.1). The difference in either SCR or SRR between the group of mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax, along with its 95% and 97.5% CI estimated using the Miettinen-Nurminen's method will be provided to assess the immune response difference.

For each strain of influenza and SARS-CoV-2, the NI of SCR or SRR will be considered demonstrated between the group of mRNA-1083 (40 μg) + Placebo and Fluzone HD + Spikevax if the lower bound of the 97.5% CI of the SCR or SRR difference is >-10% based on the prespecified NIM of 10%.

6.3.1.2 Cohort A Substudy (≥65 Years): Sensitivity, Supplementary, and Subgroup Analyses

To assess the consistency of immunogenicity response of mRNA-1083, sensitivity and subgroup analyses of the co-primary endpoints will be conducted based on the PP Immunogenicity Set. A supplementary analysis may be conducted on the Immunogenicity Set if the number of participants in the PPIS and the Immunogenicity Set differs (defined as the difference divided by the total number of participants in the PPIS) by more than 10%. The same statistical methods as for primary analysis will be used for the sensitivity, supplementary and subgroup analyses.

The primary immunogenicity endpoints may be analyzed by subgroup categories available in Table 4. Adjustment will be done for the stratification factors (age and influenza vaccine status) when applicable and 95% CIs will be calculated. If the number of participants in a subgroup category is less than 10% of sample size in the analysis set, it may be combined with other categories for the subgroup analyses.

6.3.1.3 Cohort B Substudy (≥50 to <65 Years): Primary Analyses

The primary objective of Cohort B is to evaluate the immunogenicity response between the participants receiving mRNA-1083 (40 μg) + Placebo and those receiving Fluarix + Spikevax among the adults 50 to <65 years of age. Immune responses for influenza, as measured by GM level and SCR at Day 29 by HAI assay in the group of mRNA-1083 (40 μg) + Placebo, will be

compared with those in the participants receiving Fluarix + Spikevax for all 4 influenza strains. Immune responses for SARS-CoV-2, as measured by GM level and SRR at Day 29 by PsVNA in the group of mRNA-1083 (40 μg) + Placebo, will be compared with those participants receiving Fluarix + Spikevax for the matched strain.

Five Co-primary Endpoints Based on Influenza and SARS-CoV-2 GM level at Day 29

An ANCOVA model will be carried out including the log-transformed HAI or PsVNA levels at Day 29 as the dependent variable, the treatment group as the fixed variable and log transformed baseline HAI or PsVNA levels as a fixed covariate. The model will be adjusted for the stratification factors (influenza vaccine status in the most recent influenza season: received or not received since September 2022).

The GM level will be estimated by the geometric least square mean (GLSM) from the ANCOVA model for each treatment group and corresponding 2-sided 95% CI will be provided. The GLSM and its corresponding CI in log-transformed scale estimated from the ANCOVA model will be back-transformed to the original scale to obtain an estimate of the GM level.

GMR will be estimated by the ratio of GLSM and the corresponding 2-sided 95% and 97.5% CI to assess the immune response difference between the group of mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax and presented by treatment arm (as defined in Section 6.1).

For each strain of influenza and SARS-CoV-2, the NI of GM level will be considered demonstrated between the group of mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax if the lower bound of the 97.5% CI of the GMR is >0.667 based on the prespecified NIM of 1.5.

GM level and GMR at Day 29 will be plotted.

Five Co-primary Endpoints Based on Influenza SCR and SARS-CoV-2 SRR at Day 29

Seroconversion and seroresponse are defined as follow:

Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥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 post-injection level ≥4-fold rise if Baseline is ≥ LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

The number and percentage of participants with either seroconversion (for influenza) or seroresponse (for SARS-CoV-2) postvaccination at Day 29 will be provided along with the two-sided 95% CI SCR or SRR estimated using the Clopper-Pearson method and presented by treatment arm (as defined in Section 6.1). The difference in either SCR or SRR between the group of mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax, along with its 95% and 97.5% CI estimated using the Miettinen-Nurminen's method will be provided to assess the immune response difference.

For each strain of influenza and SARS-CoV-2, the NI of SCR or SRR will be considered demonstrated between the group of mRNA-1083 (40 μg) + Placebo and Fluarix + Spikevax if the

lower bound of the 97.5% CI of the SCR or SRR difference is >-10% based on the prespecified NIM of 10%.

6.3.1.4 Cohort B Substudy (≥50 to <65 Years): Sensitivity, Supplementary and Subgroup Analyses

To assess the consistency of immunogenicity response of mRNA-1083, a sensitivity and subgroup analysis of the co-primary endpoints will be conducted based on PP Immunogenicity Set. A supplementary analysis may be conducted on the Immunogenicity Set if the number of participants in the PPIS and the Immunogenicity Set differs (defined as the difference divided by the total number of participants in the PPIS) by more than 10%. The same statistical methods as for primary analysis will be used for the sensitivity, supplementary and subgroup analyses.

The primary immunogenicity endpoints may be analyzed by subgroup categories available in Table 4. Adjustment will be done for the stratification factor (influenza vaccine status) or baseline antibody level when applicable and the 95% CIs will be calculated. If the number of participants in a subgroup category is less than 10% of sample size in the analysis set, it may be combined with other category for the subgroup analyses.

6.3.2 Secondary and Exploratory Immunogenicity Endpoints Analysis

Refer to section 6.3 of this SAP for the definition of the GM level (GMT). 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* ≠ *k*.

The 95% CIs for GM level 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.

Secondary and exploratory immunogenicity endpoints may be conducted for the subgroup categories available in Table 4 of section 6.1.

Additional descriptions will be provided by treatment arm (available in Section 6.1) for the following influenza and SARS-CoV-2 endpoints:

- Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) with the corresponding 2-sided 95% CI at each post-Baseline time point,
- For SARS-CoV-2 antibody value fold rise: Percentage of participants with >= 2-fold rise and =>4-fold rise increases from Baseline values with the corresponding 2-sided 95% CI at each post-Baseline time point,
- Percentage of participants with seroresponse (SARS-CoV-2) among participants with values above (>=) LLOQ and below (<) LLOQ values at baseline,

Percentage of participants with values below (<) LLOQ and above (>=) ULOQ values at baseline.

6.3.2.1 Cohort A Substudy (≥65 Years)

For the secondary and exploratory endpoints, GM level of HAI, MN or PsVNA with corresponding 95% CI will be provided at each timepoint. GMFR of HAI, MN or PsVNA with corresponding 95% CI at each post-Baseline timepoint over preinjection Baseline at Day 1 will be provided. For the influenza MN descriptive secondary endpoint GMT, an ANCOVA model will be carried out including the log-transformed MN levels at Day 29 as the dependent variable, the treatment group as the fixed variable and log transformed baseline MN levels as a fixed covariate. The model will be adjusted for the stratification factors (age group: 65 to <75 years of age and influenza vaccine status in the most recent influenza season: received or not received since September 2022). A subset of PPIS may be used for exploratory endpoints, including but not limited to immunogenicity analysis at Day 181. Descriptive summary statistics including median, Q1, Q3, minimum, and maximum will also be provided by treatment arm (available in Section 6.1). GM level and GMFR will be plotted at all evaluable timepoints.

6.3.2.2 Cohort B Substudy (≥50 to <65 Years)

For secondary and exploratory endpoints, GM level of HAI, MN or PsVNA with corresponding 95% CI will be provided at each timepoint. GMFR of HAI, MN or PsVNA levels with corresponding 95% CI at each post-Baseline timepoint over preinjection Baseline at Day 1 will be provided. For the influenza MN descriptive secondary endpoint GMT, an ANCOVA model will be carried out including the log-transformed MN levels at Day 29 as the dependent variable, the treatment group as the fixed variable and log transformed baseline MN levels as a fixed covariate. The model will be adjusted for the stratification factors (influenza vaccine status in the most recent influenza season: received or not received since September 2022). A subset of PPIS may be used for exploratory endpoints, including but not limited to immunogenicity analysis at Day 181. Descriptive summary statistics including median, Q1, Q3, minimum, and maximum will also be provided by treatment arm (available in Section 6.1). GM level and GMFR will be plotted at all evaluable timepoints.

6.3.2.3 Immunogenicity Analysis Across Cohort

An additional immunogenicity analysis will be performed for all participants randomized in the mRNA 1083 40 μg + Placebo treatment arm in cohorts A and B, in order to evaluate the immunogenicity response between the participants receiving mRNA-1083 included within cohort A substudy (≥65 Years) and participants receiving mRNA-1083 included within cohort B substudy (≥50 to <65 Years). Immune responses for influenza, as measured by GM level and SCR at Day 29 and Day 181 by HAI assay, and at Day 29 for MN assay, in the age group ≥65 years, will be compared with the participants in the age group ≥50 to <65 years for all 4 influenza strains. Immune responses for SARS-CoV-2, as measured by GM level and SRR at Day 29 and Day 181 by PsVNA in the in the age group ≥65 years, will be compared with the participants in the age group ≥50 to <65 years for the matched strain. Analysis will be conducted based on PP Immunogenicity Set.

An ANCOVA model will be carried out including the log-transformed HAI, MN or PsVNA levels at Day 29 or Day 181, as applicable, as the dependent variable, and the cohort as the fixed

variable and log transformed baseline HAI, MN or PsVNA levels as a fixed covariate for the GM level assessment. The model may be adjusted for the stratification factors (influenza vaccine status in the most recent influenza season: received or not received since September 2022) when applicable. The GM level will be estimated by the GLSM from the ANCOVA model for each age group and corresponding 2-sided 95% CI will be provided. GMR will be estimated by the ratio of GLSM and the corresponding 2-sided 95% CI to assess the immune response difference between the age group ≥65 years and ≥50 to <65 years and presented by age group.

The number and percentage of participants with either seroconversion (for influenza) or seroresponse (for SARS-CoV-2) postvaccination at Day 29 will be provided along with the two-sided 95% CI of SCR or SRR estimated using the Clopper-Pearson method and presented by age group. The difference in either SCR or SRR between the age group ≥65 years and ≥50 to <65 years, along with its 95% CI estimated using the Miettinen-Nurminen's method will be provided to assess the immune response difference.

6.3.3 Other Immunogenicity Exploratory Endpoints

The below exploratory analyses of immunogenicity may be performed for the Cohort A and Cohort B substudies separately:

GM level (as described in Section 6.3.2) and GMFR (compared to Day 1) to vaccine mismatched strains at all evaluable time points,

Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

6.4 Multiplicity Control

No multiplicity adjustment will be needed between the Cohort A and B substudies.

For Cohort A, a 2-sided alpha of 0.05 will be fully spent as shown in the testing sequence for co-primary and secondary endpoints in Figure 2 and described below:

Step 1 (Noninferiority): Test null hypotheses H^1_0 and H^2_0, each at a 2-sided 0.025 level.

If both null hypotheses H^1_0 and H^2_0 in Step 1 are rejected, then proceed to Step 2 below using α_1=5% level.

If only null hypotheses H^1_0 is rejected, then proceed to Step 2 below using α_1=2.5% level.

Step 2 (Superiority GM level for 4 Influenza strains): Test null hypotheses H^3_0 at the α_1 two-sided level.

If null hypotheses H^3_0 rejected, then proceed to Step 3 below:

Step 3 (Superiority GM level for 1 SARS-CoV-2 strain): Test null hypotheses H^4_0 at the α_1 two-sided level.

If null hypotheses H^4_0 rejected, and H^2_0 rejected in Step 1, then proceed to Step 4 below.

Step 4 (Superiority SCR for 4 Influenza strains): Test null hypotheses H^5_0 at a 2-sided 0.05 level.

If null hypotheses H^5_0 rejected, then proceed to Step 5 below:

Step 5 (Superiority SRR for 1 SARS-CoV-2 strain): Test null hypotheses H^6_0 at a 2-sided 0.05 level.

In the event that neither H^1_0 nor H^2_0 is rejected, then the testing sequence will stop, and all steps thereafter will not be conducted. Detailed descriptions are presented in Section 4.2 of this SAP.

All other endpoints are not controlled for multiplicity and the analyses are descriptive in nature.

Similarly for Cohort B, a 2-sided alpha of 0.05 will be fully spent, as shown in the testing sequence for coprimary and secondary endpoints in Figure 2 and described below:

Step 1 (Noninferiority): Test null hypotheses H^1_0 and H^2_0, each at a 2-sided 0.025 level.

If both null hypotheses H^1_0 and H^2_0 in Step 1 are rejected, then proceed to Step 2 below using α_1=5% level.

If only null hypotheses H^1_0 is rejected, then proceed to Step 2 below using α_1=2.5% level.

Step 2 (Superiority GM level for 4 Influenza strains): Test null hypotheses H^3_0 at the α_1 two-sided level.

If null hypotheses H^3_0 rejected, then proceed to Step 3 below:

Step 3 (Superiority GM level for 1 SARS-CoV-2 strain): Test null hypotheses H^4_0 at the α_1 two-sided level.

If null hypotheses H^4_0 rejected, and H^2_0 rejected in Step 1, then proceed to Step 4 below.

Step 4 (Superiority SCR for 4 Influenza strains): Test null hypotheses H^5_0 at a 2-sided 0.05 level.

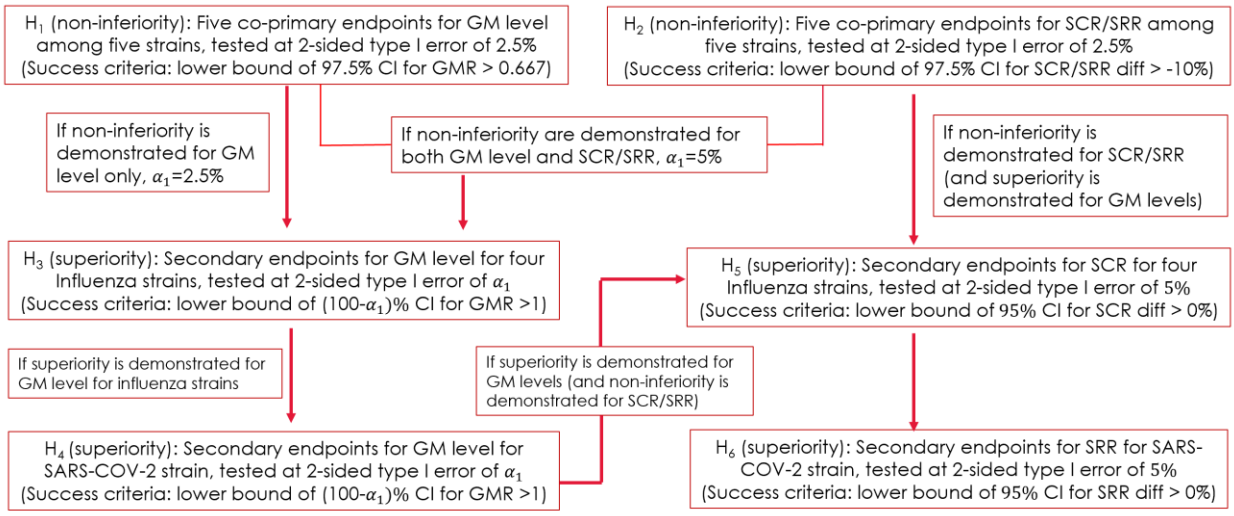
If null hypotheses H^5_0 rejected, then proceed to Step 5 below:

Step 5 (Superiority SRR for 1 SARS-CoV-2 strain): Test null hypotheses H^6_0 at a 2-sided 0.05 level.

In the event that neither H^1_0 nor H^2_0 is rejected, then the testing sequence will stop, and all steps thereafter will not be conducted. Detailed descriptions are presented in Section 4.2 of this SAP.

All other endpoints are not controlled for multiplicity and the analyses are descriptive in nature.

Figure 2 Hypotheses testing sequence for coprimary and secondary endpoints



Abbreviations: CI = confidence interval; GM = geometric mean; H = Hypothesis; SCR = seroconversion rate, SRR = seroresponse rate.

6.5 Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to withdrawal from study participation.

All safety analyses will be provided for the Cohort A and Cohort B substudies separately.

Participants will be included in the treatment arm corresponding to what they actually received and will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set, unless otherwise specified. When summarizing the number and percentage of participants with an event, participants will be presented according to the highest severity/toxicity in the summaries by severity/toxicity. Imputation rules for missing/partial dates is detailed in Appendix E.

An additional pooled safety analysis that combines the mRNA-1083 + placebo arm from the two cohorts may also be carried out. Summaries of local solicited ARs and AEs may also be presented by vaccination group and injection content received in the corresponding side/deltoid.

6.5.1 Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The eDiary will solicit daily participant reporting of ARs using a structured checklist. Participants will record such occurrences in the eDiary on the day of study injection (Day 1) and the 6 subsequent days, for a total of 7 days (through Day 7). Local ARs are expected after IM study injection. These are typically mild, transient, and self-limited and may include pain, erythema (redness),

swelling/induration (hardness) at the injection site and/or ipsilateral underarm swelling/tenderness. Systemic ARs may also occur after study injection, the majority of which are of mild to moderate in severity. Systemic ARs reported with other mRNA vaccines may include fatigue, headache, myalgia, fever, chills, arthralgia, vomiting, and/or nausea.

The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration. Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Appendix F modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS, 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded in the participant's Reactogenicity eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the clinical study or the participant being withdrawn from the clinical study by the Investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days postinjection.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

Additionally:

- 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 (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF.

6.5.1.1 Overview of Solicited ARs

An overall summary of solicited ARs up to 7 days after injection (with a toxicity grade of Grade 1 or greater) including the number and percentage of participants, by treatment arm (as defined in Section 6.1) will be presented. The number and percentage of participants experiencing any solicited local ARs and solicited systemic ARs of Grade 3 or higher will be provided as well.

6.5.1.2 Solicited ARs by Toxicity Grade

A summary of solicited ARs up to 7 days after injection (with a toxicity grade of Grade 1 or greater) by toxicity grade, including the number and percentage of participants, by treatment arm (as defined in Section 6.1) who experience the following will be presented:

- Any solicited ARs,
- Any solicited systemic AR,

Any solicited local AR,

Each individual solicited systemic and local AR,

A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR (overall, local, and systemic). An additional description for Grade 3 or Above (Grade >=3) will be provided for all above categories. Summaries of local solicited ARs will be presented by vaccination group and injection content received in the corresponding side/deltoid. A summary figure will be produced for local and systemic event rates by toxicity grade.

6.5.1.3 Solicited ARs by Onset Day

A summary of solicited ARs up to 7 days after study injection (with a toxicity grade of Grade 1 or greater) by onset day (from Day 1 through Day 7), including the number and percentage of participants, by treatment arm (as defined in Section 6.1) who experience the following will be presented:

Any solicited ARs,

Any solicited systemic AR,

Any solicited local AR,

Each individual solicited systemic and local AR,

The onset of individual solicited AR is defined as the time point after injection (Section 6.1) at which the respective solicited AR first occurred. Summaries of local solicited ARs will be presented by vaccination group and injection content received in the corresponding side/deltoid.

6.5.1.4 Characteristics of Solicited ARs

A descriptive summary of the day of onset and the duration of solicited ARs up to 7 days after study injection (with a toxicity grade of Grade 1 or greater), by treatment arm (as defined in Section 6.1) who experience the following will be presented:

Any solicited ARs,

Any solicited systemic AR,

Any solicited local AR,

Each individual solicited systemic and local AR

The onset of individual solicited AR is defined as the time point after injection (Section 6.1) at which the respective solicited AR first occurred. The duration calculation method is available in the Section 6.1 as well.

6.5.1.5 Other solicited ARs summaries

A summary of solicited ARs persisting beyond 7 days after study injection (with a toxicity grade of Grade 1 or greater) by grades, including the number and percentage of participants, by treatment arm (as defined in Section 6.1) who experience the following will be presented:

Any solicited ARs,

Any solicited systemic AR,

Any solicited local AR,

Each individual solicited systemic and local AR.

Medications taken to prevent or treat pain or fever will also be presented.

6.5.1.6 Subgroup Analysis

Analysis of solicited ARs may be conducted for subgroups as defined in Table 4 of Section 6.1 for the following summaries:

Solicited ARs by Toxicity Grade

Characteristics of Solicited ARs

Solicited ARs persisting beyond 7 days

6.5.2 Unsolicited Adverse Events

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

Unsolicited AEs include serious and nonserious AEs.

Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

An unsolicited AE is defined as any event occurring during the study not present before exposure to IP or any event already present that worsens in intensity or frequency after exposure to IP.

A MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, rash assessment or abnormal laboratory follow-up) and visits to HCPs external to the study site (eg, urgent care, primary care physician). 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.

All unsolicited AEs reported or observed during the clinical trial will be collected from start of study intervention through 28 days after injection. All AEs leading to study discontinuation,

MAAE, SAEs, and AESIs will be collected from the start of study intervention administration until through EoS or discontinuation from the clinical trial.

Unsolicited AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher and presented by MedDRA system organ class (SOC) and preferred term (PT).

Analyses of unsolicited AEs will be provided (as defined in Section 6.1):

for up to 7 days after injection,

for up to 28 days after injection and

until Day 181/EoS visit unless otherwise specified.

SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of the mRNA 1083 treatment group and then alphabetically within each 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. Only the maximum severity/toxicity level will be presented in the severity/toxicity summaries, and the strongest relationship level will be presented in the relationship summaries.

For the by-severity summaries, the toxicity grade of a solicited AR (starts outside the 7 days protocol-defined period for reporting solicited ARs) will be mapped to a severity level of Mild/Grade 1, Moderate/Grade 2, or Severe/≥ Grade 3, and the maximum severity level in the case of multiple events will be presented.

The following listings containing individual participant AEs data will be provided:

Any unsolicited AEs,

Any treatment-related unsolicited AEs,

Unsolicited serious AEs,

Unsolicited serious treatment-related AEs,

Unsolicited severe AEs

Unsolicited AEs leading to discontinued from the study,

Unsolicited MAAEs,

Unsolicited AESIs.

Treatment-emergent AEs will be flagged in all data listings.

In addition, number of participants with occurrences of selected AEs of clinical interests identified by SMQ will be summarized up to 28 Days After Injection and Throughout the Study. SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in Table 9 and Table 10. A listing of unsolicited AEs by SMQ will be provided.

6.5.2.1 Overview of Unsolicited AEs

An overall summary of unsolicited AEs, including the number and percentage of participants, by treatment arm (as defined in Section 6.1) who experience the following will be presented:

Any unsolicited AEs,

Any unsolicited serious AEs,

Any unsolicited AESI,

Any unsolicited AEs that are medically attended,

Any unsolicited AEs leading to study discontinuation,

Any unsolicited severe/≥ grade 3 AEs,

Any unsolicited AEs that are fatal.

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

6.5.2.2 AEs by System Organ Class and Preferred Term

The following summary tables of AEs will be provided by SOC and PT, sorting by frequency on the mRNA-1083 group, using frequency counts and percentages (i.e., number and percentage of participants with an event) and number of events by treatment arm (as defined in Section 6.1):

All unsolicited AEs,

All unsolicited AEs that are treatment-related,

All unsolicited serious AEs,

All unsolicited serious AEs that are treatment-related,

All unsolicited AESI,

All unsolicited AESI that are treatment-related,

All unsolicited AEs that are medically attended,

All unsolicited AEs that are medically attended that are treatment-related,

All unsolicited severe (grade ≥ 3) AEs,

All unsolicited severe (grade ≥ 3) AEs that are treatment-related,

All unsolicited AEs leading to study discontinuation,

All Unsolicited Non-Serious AEs,

Unsolicited Non-Serious Severe (grade ≥ 3) AEs.

All summary tables by SOC and PT will be provided up to 28 days after vaccine injection. In addition, all unsolicited AEs and SAEs summary tables will be provided up to 7 Days After Injection.

For all SAEs, AESIs, MAAEs, AE leading to discontinuation from the study, AE leading to death summary tables will also be provided through Day 181/EoS as well.

All unsolicited AEs and unsolicited treatment-related AEs will be summarized by SOC and PT for AEs with occurrence in ≥1% of participants in any treatment arm based on PT.

6.5.2.3 AEs by Preferred Term

The following summary tables of unsolicited AEs will be provided by PT sorting by frequency on the mRNA-1083 group:

All unsolicited AEs,

SMQ

6.5.2.4 AEs by Severity

The following summary tables of AEs will be provided by SOC, PT and the maximum severity or toxicity Grade using frequency counts and percentages by treatment arm (as defined in Section 6.1):

All unsolicited AEs,

All unsolicited AEs that are treatment-related.

6.5.2.5 Independent Cardiac Event Adjudication Committee

An independent 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. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

A summary table will be provided based on the data adjudicated by the CEAC, as the primary analysis of cardiac events.

6.5.2.6 Subgroup Analysis

Analysis of unsolicited AEs will be conducted for subgroups as defined in Table 4 of Section 6.1 for the following summaries:

Overall summary of the unsolicited AEs,

All unsolicited AEs up to 28 Days After Injection,

All unsolicited AEs up to 28 Days After Injection that are treatment-related,

All unsolicited AEs up to 28 Days After Injection by severity,

All serious unsolicited AEs up to 28 Days After Injection and Throughout the Study,

All serious unsolicited AEs that are treatment-related up to 28 Days After Injection and Throughout the Study.

6.5.2.7 Death

Total number of deaths due to any cause and time of death from injection (numeric and by time point window) may be summarized in a table. In addition, number of participants with occurrences of unsolicited AE leading to death will be summarized by SOC and PT using frequency counts and percentages. A listing of deaths including cause of death, and a listing of unsolicited AEs in participants who died will be provided.

6.5.3 Clinical Safety Laboratory Tests

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1/2 study mRNA-1083-P101 in adults.

6.5.4 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). On the day of study injection, vital sign measurements will be collected once before and at least 30 minutes after study injection. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

Following injection, any abnormal vital sign measurement should be assessed by the Investigator to determine if it meets AE reporting criteria per protocol and reported as an AE in EDC, if appropriate.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical (DHHS, 2007) available in Appendix G will be used to categorize vital sign measurements observed during this clinical trial.

Observed values and changes from pre-injection (Baseline) to post-injection (at Day 1, 30 minutes after study intervention) for all vital sign measurements will be summarized by treatment arm (as defined in Section 6.1). A toxicity grade shift table of the vital signs from pre-injection to post-injection will be provided as well.

A listing containing individual participant vital sign measurement data will be provided. Additionally, participant with any abnormal post-baseline vital sign measurement where toxicity grade (Grade 3 or higher) will be listed separately: if a participant has a vital sign result with Grade 3 or higher abnormality after injection visit, then all results for that participant will be presented in the listing.

If multiple values are collected within a post-baseline visit/timepoint, the last assessment will be used in the by-visit summary tables. Unscheduled visits (including early termination) will not be summarized in by-visit summaries of data but may contribute to either baseline or post-baseline worst-case (maximum, minimum, etc.) values when applicable.

6.5.5 Pregnancy Testing

For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before injection. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. For participants assigned female at birth and of nonchildbearing potential, the FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.

A listing containing individual participant pregnancy test results will be provided for the pregnancy tests and FSH blood levels.

6.5.6 Other Safety Data

6.5.6.1 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information.

6.5.6.2 Assessment for Respiratory Viral Infection

All participants will provide nasal 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.

6.5.6.3 Physical examination

A full physical examination will include, at a minimum, assessments of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. Height and weight will also be measured and recorded. At Screening, the body mass index will be calculated using the formula weight (kg) / (height [m])^2.

6.6 Other Exploratory Endpoints

6.6.1 Genetics

A prospective research sample, to be used for future genetic research, will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. The genetic analyses will not be covered in the plan and will be developed in a separate plan as needed.

6.6.2 Biomarkers

Transcriptomic and genomic samples will be part of the optional biomarker assessment as per the SoA 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 nasal swab samples, genetic sequences of SARS-CoV-2 or influenza strains isolated from participants' samples, and genomic and transcriptomic samples may also be evaluated. Samples will be collected according to the schedule described in the SoA in Appendix A and as detailed in the laboratory manual provided separately to sites. The biomarker analyses will not be covered in this SAP and will be developed in a separate analysis plan as needed.

6.6.3 Patient Reported Outcomes

All participants will receive eDiary prompts to complete the EQ-5D-5L daily starting at Day 1 (Baseline) through the 7 days after study injection. For Cohort B participants, the WPAI will be collected using the eDiary on Day 1 (Baseline) and Day 8.

A separate analysis plan and report will be developed for analyzing these two endpoints (EQ-5D-5L and WPAI) of patient-reported outcomes.

6.7 Planned Analyses

The statistical analyses in this clinical study will be separately planned and performed on the data collected in the 2 substudies Cohorts A and B, respectively, with each substudy independently having its own hypotheses, statistical analyses, and multiplicity control.

Throughout the study, the DSMB will conduct reviews of related SAEs at regular intervals, as outlined by the DSMB charter.

The analysis will be performed by a separate team of unblinded programmers and statisticians. More details can be found in the study data blinding plan.

6.7.1 Interim Analysis

The primary analysis of safety and immunogenicity will be performed after all participants of a given substudy have completed the Day 29 visit.

Cohort A Substudy (≥65 Years)

The primary analysis of safety, reactogenicity, and immunogenicity for Cohort A substudy will occur when all the Cohort A participants have completed the Day 29 visit.

A second interim analysis of Cohort A substudy may be performed after all the Cohort A participants have completed the Day 91 visit.

A combined analysis of Day 29/Day 91 may be performed after all the Cohort A participants have completed the Day 91 visit.

Cohort B Substudy (≥50 to <65 Years)

The primary analysis of safety, reactogenicity, and immunogenicity for Cohort B substudy will occur when all the Cohort B participants have completed the Day 29 visit.

A second interim analysis of Cohort B substudy may be performed after all the Cohort B participants have completed the Day 91 visit.

A combined analysis of Day 29/Day 91 may be performed after all the Cohort A participants have completed the Day 91 visit.

6.7.2 Final Analysis

Final analysis of all safety, immunogenicity, and efficacy data will be performed once all participants of a given substudy have complete the Day 181 (EoS) visit.

7 CHANGES FROM PLANNED ANALYSIS IN PROTOCOL

Not applicable.

8 REFERENCES

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DHHS, Department of Health and Human Services, FDA, Food and Drug Administration, Center for Biologics Evaluation and Research (US). 2007. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. [Online] September 2007. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Nauta, Jozef. 2011. *Statistics in Clinical Vaccine Trials.* s.l. : Springer, 2011.

APPENDIX A SCHEDULE OF ACTIVITIES (SOA)

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**Up to M6**
Study Visit	**SCRN[a]**	**Day 1 (Baseline)[a]**	**Day 8**	**Day 29**	**Day 91**	**Day 181 (EoS)[b]**	**USV**
Window Allowance (Days)	**-42**	**NA**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
ICF, demographics, concomitant medications, medical history[c]	X						
Inclusion/exclusion criteria	X	X					
Physical examination[d]	X	X		X			
Vital sign measurements[e]	X	X					
Pregnancy testing[f]	X	X					
Randomization		X					
Study injection (including 30-minute postdosing observation period)[g]		X					
Collection of EFS[h]		X					
Blood collection for humoral immunogenicity[i]		X[j]		X		X	
Optional blood collection for future research sample (genomics)		X[j]					
Optional blood collection for future research sample (transcriptomics)		X[j]		X			
Nasal swab for virus detection[k]		X					
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X[j]					
eDiary activation for recording solicited ARs		X					

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**Up to M6**
Study Visit	**SCRN[a]**	**Day 1 (Baseline)[a]**	**Day 8**	**Day 29**	**Day 91**	**Day 181 (EoS)[b]**	**USV**
Window Allowance (Days)	**-42**	**NA**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
Solicited AR eDiary Reporting[l]		~30 min postinjection and then daily Day 1 through Day 7					
Review of eDiary for solicited ARs		X	X				
Follow-up safety call[m]			X		X	X	
eDiary collection of EQ-5D-5L[n]		Baseline (preinjection) thereafter daily Day 2 through Day 7 postinjection					
eDiary collection of WPAI: General Health V2.0[o]		X	X				
Recording of unsolicited AEs		X	X	X			
Recording of MAAEs		X	X	X	X	X	
Recording of SAEs[p], AESIs, and AEs leading to discontinuation and any concomitant medications relevant to or for the treatment of the events	X_p	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[q]	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; C=clinic visit; COVID-19=coronavirus disease 2019; D=day; eDiary=electronic diary; EFS=Edmonton Frail Scale; EoS=end of study; EQ-5D-5L=EuroQoL 5-dimension 5-levels; FSH=follicle-stimulating hormone; HRQoL=health-related quality of life; ICF=informed consent form; ILI=Influenza-like Illness; IM=intramuscular; M=month; MAAE=medically attended adverse event; NA=not applicable; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SC=safety (phone) call; SCRN=Screening; USV=unscheduled visit; WPAI:Viral Resp=Work Productivity and Activity Impairment Questionnaire: Viral Respiratory.

a Screening and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 42-day Screening window.
b EoS is defined as completion of the last visit of the last participant in the clinical study or last scheduled procedure as shown in the SoA for the last participant in the clinical study globally.
c Verbal history is acceptable.
d A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as an MAAE.
e 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 injection (Day 1), once before and at least 30 minutes after injection. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.
f 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 FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
g All participants will be randomized to receive 2 IM injections, 1 in each deltoid muscle.
h Assessment of EFS will only be performed for participants aged 65 years and older.
i Humoral immunogenicity samples on Day 1 and Day 29 will be collected in all participants in Cohort A and Cohort B. Samples for humoral immunogenicity on Day 181 will be collected and analyzed for at least 800 participants of each cohort. These participants will require a clinic visit on Day 181. Plasma and serum from humoral immunogenicity samples will be stored for potential future use.
j Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. All blood samples must be collected prior to receipt of injection on Day 1.
k A nasal swab specimen(s) for assessment of pathogens, including influenza virus and SARS-CoV-2, will be collected any time from Day 1 through 6 months after study injection or at 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.
l The eDiary activation and entries will be recorded by the participant at approximately 30 minutes after injection 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, on the day of injection and for 6 days following injection, for a total of 7 days.
m Trained study staff will call all participants to collect information related to any AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, information on concomitant medications associated with those events, and any nonstudy vaccinations.
n The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). All participants will receive eDiary prompts to complete the EQ-5D-5L daily starting at Day 1 (Baseline) through 7 days after study injection. For Day 1 (baseline), participants should complete the EQ-5D-5L questionnaire prior to administration of the study injection.
o Cohort B only. At baseline, the WPAI questionnaire is to be completed prior to administration of the study injection.
p SAEs will be collected from the time of informed consent through Day 181 (Month 6) or EoS.
q All concomitant medications will be recorded through 28 days after injection. Additionally, nonstudy injections and certain concomitant medications will be recorded through Day 181 or EoS.

APPENDIX B STANDARDS FOR VARIABLE DISPLAY IN TLF

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. For model-based estimates, the results may be presented up to three decimal points, unless otherwise specified.

Categorical Variables

Percentages will be presented to one decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

APPENDIX C ANALYSIS VISIT WINDOWS FOR IMMUNOGENICITY ANALYSIS

Analysis visit windows will be utilized for immunogenicity assessments only. Data will be mapped using the following approach:

Step 1:

If the immunogenicity assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2:

If the immunogenicity assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 5 below.

Table 5 Analysis Visit Windows for Immunogenicity Assessments

Visit	Target Study Day	Visit Window in Study Day
Day 1	1 (Date of Injection)	1, Pre-vaccination
Day 29	29	[2, 105]
Day 181	181	≥106

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

If multiple assessments occur within both scheduled visit and unscheduled visit, the assessment collected at scheduled visit will be used.

If multiple assessments occur within a given 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.

APPENDIX D IMPUTATION RULES FOR MISSING PRIOR/CONCOMITANT MEDICATIONS AND NON-STUDY VACCINATIONS DATES

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

Missing or partially missing medication start date:

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

- If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of the IP injection.
- If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the month or the date of the IP injection - 1.
- If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of the IP injection or is missing, then use the date of the IP injection.

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

- If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of the IP injection.
- If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the year or the date of the IP injection -1.
- If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of the IP injection or is missing, then use the date of the IP injection.

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

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

Missing or partial medication stop date:

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

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

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

In summary, the prior, concomitant or post categorization of a medication is described in Table 6 below.

Table 6 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< Injection Date**	**≥ Injection Date and ≤ Injection Date + 27 days**	**> 27 Days After Injection [2]**
< Injection Date [1]	P	PC	PCA
≥ Injection date and ≤ 27 days after injection	-	C	CA
> 27 days after injection	-	-	A

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

APPENDIX E IMPUTATION RULES FOR MISSING AE DATES

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

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 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 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 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 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 injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment emergent.

Missing or partial AE end dates will not be imputed.

APPENDIX F SOLICITED ADVERSE REACTIONS AND GRADES

Table 7 Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	**Grade 0 (None)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/ induration (hardness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 10 cm	>100 mm/ >10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	**Grade 0 (None)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
Nausea/vomiting	None	No interference with activity or 1 to 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	None	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°C <100.4°F	38.0 to 38.4°C 100.4 to 101.1°F	38.5 to 38.9°C 101.2 to 102.0°F	39.0 to 40.0°C 102.1 to 104.0°F	>40.0°C >104.0°F

APPENDIX G TOXICITY GRADING OF VITAL SIGN ABNORMALITIES

Table 8 Toxicity 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 athlete

APPENDIX H ADVERSE EVENTS OF SPECIAL INTEREST BY SMQ

Table 9 Adverse Events of Special Interest by SMQ

SMQ/CMQ Name*	Type of MedDRA Query	SMQ Level	SMQ Code	Broad or Narrow Search
Anaphylactic Reaction	SMQ	1	20000021	Algorithm
				A or (B and C) or (D and (B or C))
Angioedema	SMQ	1	20000024	Narrow
Arthritis	SMQ	1	20000216	Narrow
Cardiac Arrhythmias	SMQ	1	20000049	Narrow
Arrhythmia Related Investigations, Signs and Symptoms	SMQ	2	20000051	Narrow
Cardiac Arrhythmia Terms (including bradyarrhythmias and tachyarrhythmias)	SMQ	2	20000050	Narrow
Cardiac Failure	SMQ	1	20000004	Narrow
Cardiomyopathy	SMQ	1	20000150	Narrow
Central Nervous System Vascular Disorders	SMQ	1	20000060	Narrow
Central Nervous System Haemorrhages and Cerebrovascular Conditions	SMQ	2	20000061	Narrow
Central Nervous System Vascular Disorders, not Specified as Haemorrhagic or Ischaemic	SMQ	2	20000165	Narrow
Convulsions	SMQ	1	20000079	Narrow
Demyelination	SMQ	1	20000154	Narrow
Embolic and Thrombotic Events	SMQ	1	20000081	Narrow
Embolic and Thrombotic Events, Arterial	SMQ	2	20000082	Narrow
Embolic and Thrombotic Events, Venous	SMQ	2	20000084	Narrow
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous	SMQ	2	20000083	Narrow
Guillain-Barre Syndrome	SMQ	1	20000131	Narrow
Haematopoietic Cytopenias	SMQ	1	20000027	Narrow
Haematopoietic Cytopenias Affecting More Than One Type Of Blood Cell	SMQ	2	20000028	Narrow
Haematopoietic Erythropenia	SMQ	2	20000029	Narrow
Haematopoietic Leukopenia	SMQ	2	20000030	Narrow
Haematopoietic Thrombocytopenia	SMQ	2	20000031	Narrow
Hearing and Vestibular Disorders	SMQ	1	20000170	Narrow
Hearing Impairment	SMQ	2	20000171	Narrow
Vestibular Disorders	SMQ	2	20000172	Narrow
Hypersensitivity	SMQ	1	20000214	Narrow
Immune-mediated/Autoimmune Disorders	SMQ	1	20000236	Narrow
Ischaemic Heart Disease	SMQ	1	20000043	Narrow
Myocardial Infarction	SMQ	2	20000047	Narrow

Other Ischaemic Heart Disease	SMQ	2	20000168	Narrow
Noninfectious Myocarditis/Pericarditis	SMQ	1	20000239	Narrow
Peripheral Neuropathy	SMQ	1	20000034	Narrow
Thrombophlebitis	SMQ	1	20000115	Narrow
Vasculitis	SMQ	1	20000174	Narrow

The following criteria will be used to determine anaphylactic reaction:

A term from Category A or

A term from Category B (Upper Airway/Respiratory) and a term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other or

A term from Category D (Cardiovascular/Hypotension) and at least one of the following:

- A term from Category B (Upper Airway/Respiratory) that occurred within 24 hours of each other.
- A term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.

Table 10 Algorithmic Approach for Anaphylactic Reaction:

Category	Scope	PT Search Term
A	Narrow	Anaphylactic reaction
A	Narrow	Anaphylactic shock
A	Narrow	Anaphylactic transfusion reaction
A	Narrow	Anaphylactoid reaction
A	Narrow	Anaphylactoid shock
A	Narrow	Circulatory collapse
A	Narrow	Dialysis membrane reaction
A	Narrow	Kounis syndrome
A	Narrow	Procedural shock
A	Narrow	Shock
A	Narrow	Shock symptom
A	Narrow	Type I hypersensitivity
B	Broad	Asthma
B	Broad	Bronchial oedema
B	Broad	Bronchospasm
B	Broad	Cardio-respiratory distress
B	Broad	Chest discomfort
B	Broad	Choking
B	Broad	Choking sensation
B	Broad	Circumoral oedema
B	Broad	Cough
B	Broad	Cough variant asthma

Category	Scope	PT Search Term
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema
B	Broad	Laryngospasm
B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
B	Broad	Nasal obstruction
B	Broad	Oedema mouth
B	Broad	Oropharyngeal oedema
B	Broad	Oropharyngeal spasm
B	Broad	Oropharyngeal swelling
B	Broad	Pharyngeal oedema
B	Broad	Pharyngeal swelling
B	Broad	Respiratory arrest
B	Broad	Respiratory distress
B	Broad	Respiratory failure
B	Broad	Reversible airways obstruction
B	Broad	Sensation of foreign body
B	Broad	Sneezing
B	Broad	Stridor
B	Broad	Swollen tongue
B	Broad	Tachypnoea
B	Broad	Throat tightness
B	Broad	Tongue oedema
B	Broad	Tracheal obstruction
B	Broad	Tracheal oedema
B	Broad	Upper airway obstruction
B	Broad	Vaccine associated enhanced respiratory disease
B	Broad	Wheezing

Category	Scope	PT Search Term
C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling
C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria
C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased

Category	Scope	PT Search Term
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest
D	Broad	Cardiovascular insufficiency
D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension

APPENDIX I IMMUNOGENICITY SAMPLING PLAN

I. Random Immunogenicity Subsets for MN Assay

Random Immunogenicity Subset for MN assay consists of a random sample of approximately N=150 treated participants for each treatment arm from cohort A and cohort B respectively (i.e., approximately N=300 each cohort). A total of approximately 600 (+5% attrition rate to account for any issues regarding sample availability or participant being dropped from analysis) randomly selected participants will be sent for MN assay analysis.

A stratified random sampling method will be used to select a sample of participants for the MN assay testing. The sample of participants will be randomly drawn by unblinded team according to the treatment arm assigned and the stratification factors. The sample size from each stratum will be proportional to the number of participants in each stratum in the Full Analysis Set, to represent study population. The strata are defined based on the IRT trial randomization strata as follows:

Cohort A Substudy (≥65 Years)

age groups (65 to <75 years and ≥75 years of age)

influenza vaccine status in the most recent influenza season (received or not received since September 2022).

Cohort B Substudy (≥50 to <65 Years)

influenza vaccine status in the most recent influenza season: received or not received since September 2022)

II. Random Immunogenicity Subsets for PsVNA Cross neutralization

Random Immunogenicity Subset for PsVNA cross-neutralization testing consists of a random sample of approximately N=60 treated participants for each treatment arm from cohort A and cohort B respectively (i.e., N=120 each cohort). A total of approximately 240 (+6% attrition rate to account for any issues regarding sample availability or participant being dropped from analysis) randomly selected participants will be sent for PsVNA cross-neutralization assay against variant strains (e.g. XBB.1.5 and JN.1).

A stratified random sampling method will be used to select a sample of participants for the PsVNA cross-neutralization testing to support an exploratory endpoint. The sample of participants will be randomly drawn by unblinded team according to the treatment arm assigned and the stratification factors. The sample size from each stratum will be proportional to the number of participants in each stratum in the Full Analysis Set, to represent study population. The strata are defined based on the IRT trial randomization.