ModernaTX, Inc.

mRNA-1345-P302

A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine and When Given as an Open-label Boost at 1 Year Following a Primary Dose in Adults ≥ 50 Years of Age

Statistical Analysis Plan
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DOCUMENT HISTORY

Version	Date	Description of major modifications
CCI	[redacted]	[redacted]

List of Abbreviations

Abbreviation	Definition
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical
bAb	binding antibody
BD	Booster dose
BMI	Body mass index
CDC	Center for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
DBL	Database lock
DSMB	Data safety monitoring board
eCRF	electronic case report form
EDC	Electronic data capture
eDiary	electronic diary
EoS	End of study
FAS	Full analysis set
GLSM	Geometric least squares mean
GMFR	Geometric mean fold-rise
GM	Geometric mean
GMC	Geometric mean concentration
GMR	Geometric mean titer ratio
GMT	Geometric mean titer
HA	Hemagglutination
HAI	Hemagglutination inhibition
HCP	Healthcare practitioner
HLGT	High level group term
IA	Interim analysis
IcEv	Intercurrent event
IM	Intramuscular(ly)
IP	investigational product
IRT	Interactive Response Technology
LB	Lower bound
LLOQ	Lower limit of quantification

MAAE	Medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
PostBD	Post booster dose
PP	Per-protocol
PreBD	Prior to booster dose
PT	Preferred term
RSV	Respiratory Syncytial Virus
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Seroconversion rate
SD	Standard deviation
SOC	System organ class
SMQ	Standardized MedDRA Queries
SRR	Seroresponse rate
Supportive PP Set	Supportive PP Set for Group 1 and Group 2 Comparison
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This SAP is based on CSP (Amendment 5, dated on 16-June-2023) and approved eCRF (version 16.038, dated on 01-August-2023).

In addition to the information presented in the statistical consideration sections of the protocol (Sections 2.8, 3.8, and 4.8) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan which are not "principal" in nature and result from information that was not available at the time of protocol finalization. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

Study mRNA-1345-P302 is a Phase 3, randomized, observer-blind, study to evaluate safety, tolerability, and immunogenicity of mRNA-1345, an mRNA vaccine targeting RSV, when given alone or coadministered with a seasonal influenza vaccine or SARS-CoV-2 vaccine and when given as an open-label boost at 1 Year following a primary dose in adults ≥ 50 years of age.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis. SAS Version 9.4 or higher will be used.

In this document, injection and dose are used interchangeably.

2. Part A

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Primary Safety Objective

The primary safety objective of the study is to evaluate the safety and tolerability of the mRNA-1345 vaccine coadministered with a seasonal influenza vaccine (Afluria Quadrivalent).

2.1.1.2. Primary Immunogenicity Objective

The primary immunogenicity objectives are:

1) To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A
2) To evaluate the impact of coadministered RSV vaccine on the immune response to influenza

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Immunogenicity Objectives

The key secondary immunogenicity objectives are:

- To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-B
- To evaluate the impact of coadministered RSV vaccine on the immune response to influenza based on seroconversion from baseline

2.1.2.2. Other Secondary Immunogenicity Objectives

The other secondary immunogenicity objectives are:

- To evaluate the Ab response to mRNA-1345 with and without a seasonal influenza vaccine (Afluria Quadrivalent)
- To evaluate the Ab response to seasonal influenza vaccine (Afluria Quadrivalent) with and without mRNA-1345

2.1.3. Exploratory Objectives

The exploratory objectives, which may be performed, are as follows:

- To further characterize the immune response across study vaccines

2.2. Study Endpoints

2.2.1. Primary Endpoints

2.2.1.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Numbers and percentages of participants with solicited local and systemic ARs over the 7 days post-injection
- Numbers and percentages of participants with unsolicited AEs through 28 days post-injection
- Numbers and percentages of participants with MAAEs, SAEs, AESIs, and AEs leading to withdrawal from Day 1 (baseline) to Day 181/EoS

2.2.1.2. Primary Immunogenicity Endpoints

The primary immunogenicity objectives will be evaluated by the following coprimary endpoints:

- GMT of serum RSV-A nAbs at Day 29
- SRR in serum RSV-A nAbs at Day 29. Seroresponse for RSV-A nAbs is defined as a post-injection titer is ≥ 4x LLOQ if baseline is < LLOQ, or a ≥ 4-fold rise from baseline in post-baseline titer if baseline is ≥ LLOQ.

- GMT of serum anti-HA Abs as measured by HAI assay for influenza A strains and B strains at Day 29

2.2.2. Secondary Endpoints

2.2.2.1. Key Secondary Immunogenicity Endpoints

The key secondary immunogenicity objectives will be evaluated by the following endpoints:

- GMT of serum RSV-B nAbs at Day 29
- SRR in serum RSV-B nAbs at Day 29. Seroresponse is defined in the same way as for RSV-A nAbs.
- SCR in seasonal influenza anti-HA Abs for influenza A and B strains at Day 29. Seroconversion for an influenza strain is defined as a post-injection titer ≥ 1:40 if baseline is < 1:10, or a ≥ 4-fold rise from baseline in post-baseline titer if baseline is ≥ 1:10.

2.2.2.2. Other Secondary Immunogenicity Endpoints

The other secondary immunogenicity objectives will be evaluated by the following endpoints:

- GMT and GMFR of post-injection/baseline titers to RSV-A nAbs up to Day 181/EoS
- GMT and GMFR of post-injection/baseline titers to RSV-B nAbs up to Day 181/EoS
- SRR and proportion of participants with ≥ 2-fold increases in RSV-A nAb titers up to Day 181/EoS. A ≥ z-fold increase in RSV A nAb titers is defined as a post-injection titer is ≥ z x LLOQ if baseline is < LLOQ, or a ≥ z-fold increase from baseline in post-injection titers if baseline is ≥ LLOQ.
- SRR and proportion of participants with ≥ 2-fold increases in RSV-B nAb titers up to Day 181/EoS. A ≥ z-fold increase in RSV-B nAb titers is defined in the same way as for RSV-A nAbs.
- SCR and proportion of participants with ≥ 2-fold increases at Day 181/EoS in seasonal influenza anti-HA Abs measured by HAI assay. A ≥ z-fold increase in anti-HA Ab titers is defined in the same way as for RSV-A nAbs.
- GMT and GMFR of post-injection/baseline titers to serum seasonal influenza anti-HA Abs as measured by HAI assay up to Day 181/EoS.

2.2.3. Exploratory Endpoints

- GMC and GMFR of post-injection/baseline concentration to RSV bAbs up to Day 181/EoS
- Proportions of participants with ≥ 2-fold and ≥ 4-fold increases in RSV bAb concentration up to Day 181/EoS. A ≥ z-fold increase in RSV bAb concentration is defined in the same way as for RSV-A nAbs.
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

2.3. Study Design

2.3.1. Overall Study Design

Part A is a Phase 3, randomized, observer-blind study to evaluate safety, tolerability, and immunogenicity of mRNA-1345, an mRNA vaccine targeting RSV, when given alone or coadministered with a seasonal influenza vaccine (Afluria Quadrivalent) in adults ≥ 50 years of age.

All participants will participate in a Screening period (up to 14 days before Day 1), treatment period (vaccine and/or placebo administration on Day 1 [Baseline]), and a follow-up period (up to 6 months after vaccination). The SoA is provided in Appendix F.

The study will enroll approximately 1620 medically stable adults ≥ 50 years of age. On Day 1, each participant will receive 2 injections administered IM, one in each arm, in the deltoid muscle. Participants will be randomized as shown in Table 1 to receive either 1) mRNA-1345 ([CCI] µg) + placebo (0.9% sodium chloride [normal saline]); 2) mRNA-1345 ([CCI] µg) + Afluria Quadrivalent; or 3) Afluria Quadrivalent + placebo. Randomization will be stratified by age (50 to 59 years, 60 to 74 years, and ≥ 75 years). The study will target enrollment of approximately 20% of participants 50 to 59 years of age.

Table 1: Randomized Groups

Group Name	Sample Size	Vaccine Administered
Group 1	420	mRNA-1345 ([CCI] µg) + placebo in contralateral arms
Group 2	600	mRNA-1345 ([CCI] µg) + Afluria Quadrivalent in contralateral arms
Group 3	600	Afluria Quadrivalent + placebo in contralateral arms

Participants will have a total of 8 visits/safety telephone calls. At the dosing visit on Day 1, participants will be instructed how to document and report solicited ARs in a provided eDiary. Solicited ARs will be assessed from Day 1 through Day 7 (the day of injection and the following 6 days), and local solicited ARs will be assessed separately for each injection site. Unsolicited AEs will be assessed from Day 1 through Day 28 (the day of injection and the following 27 days). SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be assessed from Day 1 through Day 181/EoS.

Blood sample collection for humoral immunogenicity will occur on Day 1, Day 29, and Day 181/EoS. The samples will be processed and analyzed as per the Laboratory Manual. The Day 8 visit (Visit 2) may be either at the study site or a via a telephone call. The study site staff will perform scheduled safety telephone calls to participants on Day 57, Day 91, Day 121, and Day 151 to collect AEs, MAAEs, AESIs, AEs leading to withdrawal, SAEs, and information about concomitant medications related to those events and receipt of non-study vaccinations.

An IRT error in Part A conduct was identified in March 2023. More details are provided in Section 2.3.4.

2.3.2. Statistical Hypothesis

The immunogenicity primary objectives are to evaluate the effect of coadministered influenza vaccine on the immune response to RSV-A virus and influenza A and B strains included in Afluria Quadrivalent. There are 6 co-primary endpoints to support the primary objectives.

Primary Objective to Evaluate the Impact on the Immune Response to RSV-A:

Co-primary endpoints based on GMT at Day 29:

The null hypothesis H_0^1: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by GMT at Day 29 using RSV-A nAb assay, is inferior compared with that in participants who received mRNA-1345 plus placebo. The noninferiority in the GMT of RSV-A nAbs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of GMR of ruling out 0.667 (i.e., LB > 0.667), using noninferiority margin of 1.5. The GMR is the ratio of the GMT of RSV-A nAbs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with the GMT of RSV-A nAbs in participants who received mRNA-1345 plus placebo.

Co-primary endpoints based on Seroresponse Rate at Day 29:

The null hypothesis H_0^2: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Afluria, as measured by SRR of RSV-A nAbs at Day 29, is inferior compared with that in participants who received mRNA-1345 plus placebo. The noninferiority in the SRR in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of the SRR difference (coadministered group − mRNA-1345 plus placebo) of ruling out -10% (i.e., LB > -10%), using noninferiority margin of 10%.

Primary Objective to Evaluate the Impact on the Immune Response to Influenza:

Co-primary endpoints based on GMT at Day 29:

The null hypotheses H_0^3 to H_0^6: immunogenicity response to Afluria Quadrivalent in participants who received Afluria Quadrivalent coadministered with mRNA-1345, as measured by GMT of anti-HA Abs for each of the 4 influenza strains at Day 29 using HAI assay, is inferior compared to that in participants who received Afluria Quadrivalent plus placebo. For each of the 4 influenza strains, the noninferiority in the GMT in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received Afluria Quadrivalent plus placebo will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB > 0.667), using noninferiority margin of 1.5. The GMR is the ratio of the GMT of anti-HA Abs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with the GMT of anti-HA Abs in participants who received Afluria Quadrivalent plus placebo.

Key Secondary Objective to Evaluate the Impact on the Immune Response to RSV-B:

Key secondary endpoint based on GMT at Day 29:

The null hypothesis H_0^7: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by GMT at Day 29 using RSV-B nAb assay, is inferior compared with that in participants who received mRNA-1345 plus placebo. The noninferiority in the GMT of RSV-B nAbs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB > 0.667), using noninferiority margin of 1.5. The GMR is the ratio of the GMT of RSV-B nAbs in participants who received mRNA-1345 coadministered with Afluria compared with the GMT of RSV-B nAbs in participants who received mRNA-1345 plus placebo.

Hypothesis 7 will be assessed once all the primary hypotheses 1 to 6 are demonstrated.

Key secondary endpoint based on SRR at Day 29:

The null hypothesis H_0^8: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by SRR of RSV-B nAbs at Day 29, is inferior compared with that in participants who received mRNA-1345 plus placebo. The noninferiority in SRR of RSV-B nAbs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of the SRR difference (coadministered group − mRNA-1345 plus placebo) of ruling out -10% (i.e., LB > -10%), using noninferiority margin of 10%.

Hypothesis 8 will be assessed once all the primary hypotheses and the first key secondary hypothesis (i.e., hypothesis 1 to 7) are demonstrated.

Key Secondary Objective to Evaluate the Impact on the Immune Response to Influenza Based on Seroconversion from Baseline:

Key secondary endpoint based on SCR at Day 29:

The null hypotheses H_0^9 to H_0^{12}: immunogenicity response to Afluria Quadrivalent in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by SCR of anti-HA Abs for each influenza strain at Day 29 using HAI assay, is inferior compared with that in participants who received Afluria plus placebo. The noninferiority in SCR in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that in participants who received Afluria Quadrivalent plus placebo will be demonstrated by the LB of the 95% CI of the SCR difference (coadministered group − Afluria Quadrivalent plus placebo) of ruling out -10% (i.e., LB > -10%), using noninferiority margin of 10%.

Hypotheses 9 to 12 will be assessed once all the primary hypotheses and the key secondary hypotheses (i.e., hypothesis 1 to 8) are demonstrated.

The hierarchical order for the hypotheses to be tested is also indicated in Figure 1

2.3.3. Sample Size and Power

The study will plan to randomize approximately 1620 participants, with approximately 420 participants receiving mRNA-1345 + placebo (Group 1), 600 participants receiving mRNA1345 + Afluria Quadrivalent (Group 2), and 600 participants receiving Afluria Quadrivalent + placebo (Group 3).

With approximately 420 participants exposed to mRNA-1345 plus placebo, the study has approximately 95% probability to observe at least 1 participant with an AE at a true 0.7% AE rate. With approximately 600 participants exposed to mRNA-1345 plus Afluria Quadrivalent and Afluria Quadrivalent plus placebo, respectively, the study has approximately 95% probability to observe at least 1 participant with an AE at a true 0.5% AE rate.

Sample Size and Power for the primary immunogenicity endpoints:

Assuming approximately 10% of participants are ineligible to be included in the PP Set. The overall power considering meeting the primary objectives to evaluate the immune responses to RSV-A and influenza is 90%. Sample size justification for the co-primary immunogenicity endpoints is shown in Table 2.

Table 2: Sample Size Justification for the Co-primary Immunogenicity Endpoints

Primary Endpoint	Number of Evaluable Participants (with 10% ineligible for Per-protocol Set)	α	Standard Deviation	GMR/SRR Assumed	NI Margin	Power
mRNA-1345 Noninferiority (2-sided test)						
Day 29 GMT Coadministration (Group 2) vs. alone (Group 1)	378(Group 1) 540(Group 2)	0.05	1.5	GMR=1	1.5	98%
Day 29 SRR Coadministration (Group 2) vs. alone (Group 1)	378 (Group 1) 540 (Group 2)	0.05		SRR=0.8 in both groups	10%	96%
Afluria Quadrivalent Noninferiority (2-sided test) for Each Influenza Strain						
Day 29 GMT Coadministration (Group 2) vs. alone (Group 3)	540 (Group 2) 540 (Group 3)	0.05	1.5	GMR=1	1.5	99%
Overall power to show noninferiority of the primary immunogenicity endpoints						90%

With 540 participants to be included in PP Set in mRNA-1345 + Afluria Quadrivalent (Group 2) and 378 participants to be included in PP Set in mRNA-1345 + placebo (Group 1):

- There is at least 98% power to demonstrate the noninferiority of the immune response to RSV-A, as measured by GMT of RSV-A nAb in participants receiving mRNA-

1345 plus Afluria Quadrivalent compared with that in mRNA-1345 plus placebo group, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The standard deviation of the natural log-transformed level is assumed to be 1.5.

- There is at least 96% power to demonstrate the noninferiority of the immune response, as measured by SRR of RSV-A nAbs at Day 29 in participants receiving mRNA-1345 plus Afluria Quadrivalent compared with that in mRNA-1345 plus placebo group, at a 2-sided alpha of 0.05, assuming an SRR of RSV-A nAbs of 80% in both groups (a true SRR difference is 0), and a noninferiority margin of 10%.

With 540 participants to be included in PP Set in either mRNA-1345 plus Afluria Quadrivalent group (Group 2) or Afluria Quadrivalent plus placebo group (Group 3):

- There is at least 99% power to demonstrate noninferiority of the immune response to each of the 4 influenza strains, as measured by GMT of influenza anti-HA Abs for each strain in participants receiving mRNA-1345 plus Afluria Quadrivalent compared with that in Afluria Quadrivalent plus placebo group, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The standard deviation of the natural log-transformed level is assumed to be 1.5.

Sample Size and Power for the key secondary immunogenicity endpoints:

With 540 and 378 participants to be included in PP Set in mRNA-1345 plus Afluria Quadrivalent group (Group 2) and mRNA-1345 + placebo (Group 1), respectively:

- There is at least 98% power to demonstrate the noninferiority of the immune response to RSV-B, as measured by GMT of RSV-B nAb in participants from Group 2 compared with that from Group 1, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The standard deviation of the natural log-transformed level is assumed to be 1.5.
- There is at least 96% power to demonstrate the noninferiority of the immune response, as measured by SRR of RSV-B nAbs at Day 29 in participants from Group 2 compared with that from Group 1, at a 2-sided alpha of 0.05, assuming a SRR of 80% in both groups (a true SRR difference is 0) and a noninferiority margin of 10%.

With 540 participants to be included in PP Set in either mRNA-1345 plus Afluria Quadrivalent group (Group 2) or Afluria Quadrivalent plus placebo group (Group 3):

- There is approximately 95% power to demonstrate the noninferiority of the immune response to each of the 4 influenza strains, as measured by SCR of influenza anti-HA

Abs for each strain at Day 29 in participants from Group 2 compared with that from Group 3, at a 2-sided alpha of 0.05, assuming an SCR of 70% in both groups (a true SCR difference is 0) and a noninferiority margin of 10%.

- Under the same assumptions for each strain, the overall power to demonstrate the noninferiority of the immune response to 4 influenza strains is approximately 80%.

2.3.4. Randomization

The randomization will be in a blinded manner using a centralized IRT, in accordance with pre-generated randomization schedules.

The study will enroll approximately 1620 medically stable adults ≥ 50 years of age. Participants will be randomized with a ratio of 7:10:10 to receive either 1) mRNA-1345 + placebo (Group 1, 420 participants); 2) mRNA-1345 + Afluria Quadrivalent (Group 2, 600 participants); or 3) Afluria Quadrivalent + placebo (Group 3, 600 participants). Randomization will be stratified by age (50 to 59 years, 60 to 74 years, and ≥ 75 years). The study will target enrollment of approximately 20% of participants 50 to 59 years of age. Randomization details is described in Section 2.3.1.

An IRT error

On 07-March-2023, the Sponsor was informed of an error in the randomization ratio in Part A. The IRT vendor inadvertently inactivated the enrollment for Group 1 when 959 participants were randomized in Part A as part of a system build to fix an unrelated issue on 25-May-2022. Group 1 remained inactive until 25-Jul-2022 while the enrollment of Part A was completed on 09- June-2022. As a result, approximately 250 participants, instead of protocol planned 420 participants, were randomized in Group 1. This IRT error caused an under enrollment of around 170 participants in Group 1 and an over enrollment in Group 2 and 3; and the actual ratio for participants randomized in the three Groups was approximately 5:14:14.
The above information was received after the EDC database of Part A was locked but before the selected Sponsor and CRO personal, as defined by the study Data Blinding Plan, are to be unblinded to perform the analyses, and before the immunogenicity data become available. The assessment of actual randomization ratio was also conducted in a blinded fashion.

2.3.5. Blinding and Unblinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with certain exceptions, please refer to Section 2.5.2 of the protocol and Data Blinding Plan for details.

Planned analyses are described in Section 2.5.6 of the SAP and Section 2.8.6 in the protocol. At the primary analysis, pre-identified Sponsor team members and selected CRO team members as specified in the study Data Blinding Plan will be unblinded to conduct the analyses. Meanwhile, a separated blinded biostatistics and programming team will be in place until the database lock for the Final Analysis. Participants and investigators will remain blinded until the end of this study.

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

2.4. Analysis Populations

Analysis populations for statistical analyses are Randomization Set, Full Analysis Set, PP Set, Supportive PP Set, Solicited Safety Set, and Safety Set.

2.4.1. Randomization Set

The Randomization Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be included in the vaccination group to which they are randomized.

2.4.2. Full Analysis Set

The FAS consists of all randomized participants who receive any study injection. Participants will be analyzed according to the vaccination group to which they are randomized.

2.4.3. Per-protocol Set

PP Set

The PP Set consists of all participants in the FAS who receive the assigned study injections according to protocol, comply with immunogenicity blood sampling to have a baseline and at least one Day 29 post-injection assessment within the visit window of study day [22, 43], and have no major protocol deviations that impact the immune response.

The PP Set will be the primary population used for the analysis of immunogenicity data, and Participants will be included in the vaccination group to which they are randomly assigned.

Supportive PP Set

The Supportive PP Set consists of all Group 1 and Group 2 participants in the PP Set from mRNA-1345-P302 and participants from mRNA-1345-P301 who are in the Per-protocol Immunogenicity Set, received one injection of mRNA-1345 ([redacted] µg) during April to June of 2022, and were in the Phase 3 segment from U.S sites. Please refer to Section 5.5 of mRNA-1345-P301 SAP for detailed definition of the Per-protocol Immunogenicity Set. The Supportive PP Set will be the analysis set for a supportive analysis of the primary immunogenicity endpoints of RSV-A nAbs and the key secondary immunogenicity endpoints of RSV-B nAbs to mitigate the IRT error as indicated in Section 2.3.4. The participants from mRNA-1345-P301 and the Group 1 participants from mRNA-1345-P302 will be pooled together and compared with the Group 2 participants from mRNA-1345-P302.

2.4.4. Safety Set

The Safety Set consists of all randomized participants who receive any study injection. The Safety Set will be used for all analyses of safety except for the solicited ARs.

Participants will be included in the vaccination group corresponding to the study injections that they actually received.

2.4.5. Solicited Safety Set

The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited ARs data, i.e., have at least one post-baseline solicited safety assessment.

The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study injections that they actually received.

2.5. Statistical Analysis

2.5.1. General Considerations

The Schedule of Assessments is provided in Appendix F.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For the summary statistics of all numerical variables, unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

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

Baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first injection, unless otherwise specified. For immunogenicity tests, the baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date of the first injection (Day 1). If there are multiple valid results on the same date, the largest value will be considered in the immunogenicity baseline derivation.

Study day relative to the Day 1 injection will be calculated as below:

a) Study day prior to the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection (resulting in negative study day).

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

For GMT and GMC calculation, antibody values reported as below the LLOQ will be replaced by 0.5 × LLOQ and antibody values greater than the ULOQ will be converted to the ULOQ.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In the derivation of baseline measurements.
- In scheduled visit windows per specified visit windowing rules.
- In individual participant data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B, Table 5.

Incomplete/missing data:

- Imputation rules for missing dates of prior/concomitant medications and non-study vaccinations are provided in Appendix C.
- Imputation rules for missing dates of prior/concomitant 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.

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1345 ([CCI] µg) + placebo
- mRNA-1345 ([CCI] µg) + Afluria Quadrivalent
- Afluria Quadrivalent + placebo

If a subject receives any dose of mRNA-1345, regardless of the vaccination group the subject is randomized to, the subject will be included in the actual vaccination group received (mRNA-1345 + placebo or mRNA-1345 + Afluria Quadrivalent) for safety and reactogenicity analyses.

All analyses and data summaries/displays for disposition, demographics and baseline characteristics, safety and immunogenicity will be provided by vaccination group using appropriate analysis population, unless otherwise specified. Local solicited adverse reactions will be also summarized by injection content (mRNA-1345, Placebo and Afluria Quadrivalent).

2.5.2. Background Characteristics

2.5.2.1. Participant Disposition

The number and percentage of participants in the following categories (analysis sets defined in Section 2.4) will be summarized by vaccination group as defined in Section 2.5.1 based on Randomization Set:

- Randomization Set
- Full Analysis Set
- Per-protocol Set
- Safety Set
- Solicited Safety Set

The percentages will be based on the number of participants in the Randomization Set (as randomized), except that for the Safety Set and Solicited Safety Set in which the percentages will be based on the number of participants in the Safety Set (as treated).

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

- Number of participants screened

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

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

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

- Received any study injection
- Completed the study
- Prematurely discontinued the study and the reason for discontinuation

The number and percentage of participants by IRT randomized stratum (50 to 59 years, 60 to 74 years and ≥ 75 years) will be presented by vaccination group. Also, the concordance between IRT randomized stratum and CRF derived stratum will be tabulated by vaccination group.

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

A participant, who has completed the last scheduled procedure on Day 181 (i.e., 6 months after administration of the study injections on Day 1), is considered to have completed the study.

2.5.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), BMI (kg/m^2). The number and percentage of participants will be provided for categorical variables such as randomized and actual age group (50 to 59 years, 60 to 74 years, and ≥ 75 years), gender and race. The summaries will be presented by vaccination group as defined in Section 2.5.1. The summaries will be provided separately based on the Randomized Set, FAS, Safety Set, Solicited Safety Set, PP Set, and Supportive PP Set.

In the Supportive PP Set, participants will be presented by the vaccination group as Group 1 participants from mRAN-1345-P302, participants from mRNA-1345-P301, and Group 2 participants from mRNA-1345-P302. Group 1 participants from mRAN-1345-P302 and participants from mRNA-1345-P301 will also be pooled together as an “Adjusted Group 1” in the summary. The descriptive statistics for age (as a continuous variable), age group (50 to 59

years, 60 to 69 years, 70-79 years, and ≥ 80 years), weight, height, BMI, gender, and race will be presented by the vaccination group.

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

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

2.5.2.3. Medical History

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the mRNA-1345 ([CCI] µg) + Afluria Quadrivalent group and then alphabetically within SOC.

Number of events and number of participants with selected medical conditions, as indicated in Appendix K, Table 17, will also be summarized by SOC, HLGT, and PT for each vaccination group.

The number and percentage of participants with any medical history will be also summarized by SOC and PT based on the Supportive PP Set and presented by the vaccination group as indicated in Section 2.5.2.2. PT will be displayed in descending order of frequency of the "Adjusted Group 1" and then alphabetically within SOC.

Medical history data will be coded by SOC, HLGT (for selected medical conditions), and PT according to the MedDRA (Version 25.0 or higher).

2.5.2.4. Prior and Concomitant Medications

Prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent will be recorded in the participant's eCRF. Medications and non-study vaccinations taken/received by the participant during the study will be recorded in the eCRF for the information as specified in Section 2.5.5.2 of the study protocol. Prior and concomitant medications will be coded using the WHO-DD. The summary of concomitant medications will be based on the Safety Set. Imputation rules for missing/partial dates for medications is detailed in Appendix C.

For the purpose of analysis, a medication taken prior to the injection date, regardless of whether the end date is before or after the injection date, is defined as "prior"; if the medication is taken between the injection date and up to 28 days after the injection date (inclusive), then it is

considered “concomitant”, regardless of whether the start date is before or after the injection date; if the medication is taken after 28 days post injection (i.e. end date of the medication is after 28 days post injection or ongoing after 28 days after IP injection), it is a “post” medication.

An overall summary table of concomitant medications and non-study vaccinations will be provided to present the number and percentage of participants who take the following:

- Any concomitant medications and non-study vaccinations within 7 days post injection
- Any concomitant medications and non-study vaccinations within 28 days post injection
- Any non-study vaccinations within 7 days post injection
- Any non-study vaccinations within 28 days post injection
- Any prophylactic antipyretics or analgesics medication within 28 days post injection
- Any antipyretic or analgesic medication within 28 days post injection

A summary table of concomitant medications and non-study vaccinations within 28 days post injection will be provided by ATC level 2 and preferred term. Preferred terms will be displayed in descending order of frequency of the mRNA-1345 ([CCI] µg) + Afluria Quadrivalent group. A separate summary table of non-study vaccinations within 7 days post injection will be also provided by preferred term.

An overall summary of medications taken to prevent or treat fever or pain within 7 days post injection will be also provided based on Solicited Safety Set. The summary will be based on participants’ responses to the eDiary questions regarding whether they have taken any antipyretic or analgesic medications to prevent or treat fever/pain within 7 days post injection.

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

2.5.2.5. Concomitant Procedures/Surgeries

Procedures and/or surgeries data will be coded by SOC and PT using the MedDRA. Imputation rules for missing/partial dates of procedures/surgeries are detailed in Appendix D.

For the purpose of analysis, a procedure/surgery occurred prior to the injection date (including cases where the procedure/surgery date is completely missing) is defined “prior”; if the procedure/surgery is performed on or after the injection date and on or prior to 28 days after the injection date, then it is considered “concomitant”; otherwise, it is a “post” procedure/surgery.

The number and percentage of participants with any concomitant procedure/surgery will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple procedures/surgeries within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the mRNA-1345 ([redacted] µg) + Afluria Quadrivalent group and then alphabetically within SOC.

Concomitant and post procedures/surgeries will be presented in a listing.

2.5.2.6. Study Exposure

Summary of time on study in days will be presented by vaccination group in Safety Set, PP Set and Supportive PP Set for the following:

- Time on study from randomization in days: calculated as date of study discontinuation/completion – date of randomization +1.
- Time on study from injection in days: calculated as date of study discontinuation/completion – date of Day 1 injection +1.

In the Supportive PP Set, the duration will be presented by the vaccine group as indicated in Section 2.5.2.2. The number and percentage of participants of receiving initial mRNA-1345 in each calendar month (April-2022, May-2022, and June-2022) will also be provided.

Study injection detail as well as participant with dosing error will be also presented in a listing.

2.5.2.7. Significant Protocol Deviations

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

The number and percentage of the participants with each significant protocol deviation type will be provided by vaccination group on the Randomization Set.

Selected significant protocol deviations impact critical or key study data (also referred to as major protocol deviations in the protocol), and participants with such deviations will be excluded from the PP Set for immunogenicity analyses; such major protocol deviations will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from PP Set for immunogenicity will be summarized.

2.5.2.8. COVID-19 Impact

An individual data listing on COVID-19 impact will be provided for the Randomization Set and it will include which visit(s)/assessment(s) has (have) been missed due to COVID-19, along with the specific relationship to COVID-19.

2.5.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to study discontinuation, vital signs, and physical examination findings. Solicited ARs will be coded according to the MedDRA for AR terminology and unsolicited AEs will be coded by SOC and PT according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used in this study.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group as defined in Section 2.5.1, unless otherwise specified.

2.5.3.1. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the participant in eDiary. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 2.7.1.1 of the study protocol). Participants will record such occurrences in an eDiary from Day 1 through Day 7 (i.e., the day of injection and 6 subsequent days). Local solicited ARs will be recorded separately for each injection site (left and right arm). Severity grading of reactogenicity will occur automatically based on participant entry in the eDiary according to the grading scales presented in Table 4 of the study protocol from the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS 2007).

If a participant had a Grade 1 or higher AR during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity eCRF. If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event on the Reactogenicity eCRF. If the participant reported an event that started after the solicited period (i.e., after Day 7), it should be recorded as an AE on the AE eCRF.

The following local ARs for each injection site (left and right arm) will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the injection arm. The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aches in several joints), nausea/vomiting, chills, and fever.

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

All analyses of solicited ARs will be provided by vaccination group as defined in Section 2.5.1 based on the Solicited Safety Set. Summaries of local solicited ARs will be also presented by vaccination group and injection content (mRAN-1345, Afluria Quadrivalent, and Placebo).

The number and percentage of participants with any solicited ARs, any solicited local ARs and any solicited systemic ARs during the 7-day follow-up period after injection will be summarized by vaccination group with a 2-sided 95% exact CI using the Clopper-Pearson method. Refer to Safety Estimand 4a in Appendix I, Table 9.

The following summaries for solicited ARs will be presented by vaccination group:

- The number and percentage of participants who reported each individual solicited AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after injection will be summarized by severity grade. For each local solicited AR, the summary will be based on the highest grade of the ARs observed from both injection sites (left and right arm).
- The number and percentage of participants who reported each individual solicited AR will be summarized by the onset day relative to the injection (Day 1 through Day 7). The onset day of an individual solicited AR is defined as the time point after injection at which the respective solicited AR first occurred. For each local solicited AR, the summary will be based on the earliest onset day of the ARs from both injection sites (left and right arm).
- The duration (days) of each solicited AR will be summarized descriptively. The duration will be calculated as: end date of solicited AR event – reaction start date of solicited AR event +1, no matter if it is intermittent or continued or if the solicited AR continues beyond 7 days. For each local solicited AR, the summary will be based on the longest duration of the ARs observed from both injection sites (left and right arm).
- The number and percentage of participants who reported any solicited ARs that continue beyond 7 days post-injection will be summarized.

The number and percentage of participants who reported each individual solicited AR summarized by severity grade and by onset day will be also presented separately for local solicited ARs only by vaccination group and injection content.

Bar plots may be created to display the percentage of participants who reported solicited AR.

The summaries of solicited ARs by vaccination group and local solicited ARs by vaccination group and injection content may be provided for the following subgroup:

- Age group (50 to 59 years, 60 to 74 years, ≥ 75 years)
- Age group (50 to 59 years, ≥ 60 years)
- Sex (male, female)
- Race (White, Black, Asian, or other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races])

These summaries may be provided for additional subgroups of selected baseline characteristics.

2.5.3.2. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial participant administered a medicinal drug product and which does not necessarily have a causal relationship with this treatment. AEs will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to an HCP.

A TEAE is defined as any event occurring during the study not before exposure to study vaccine. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

An unsolicited TEAE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (i.e., 7 days after study vaccine administration). For analysis and reporting purpose, unsolicited TEAEs will include the following:

- TEAEs that are reported by participants and recorded on the AE eCRF
- Solicited ARs that meet SAE criteria and are recorded on the Reactogenicity eCRF

Unsolicited AEs will be collected for up to 28 days after injection; SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be collected throughout the study. Unsolicited TEAEs will be summarized up to 28 days after injection unless otherwise specified. Additionally, SAEs, MAAEs, AESIs and AEs leading to study discontinuation will be summarized throughout the study (up to Day 181/EoS). Refer to Safety Estimand 4b in Appendix I, Table 10.

All summary tables (except for the overall summary of TEAEs) for unsolicited TEAEs will be presented by SOC and PT (or by PT). SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1345 ([CCI] µg) + Afluria Quadrivalent group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once.

For the by severity summaries, the toxicity grade of a solicited AR meeting SAE criteria after injection 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.

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

The number of events and number of participants reported occurrence of selected TEAEs of clinical interests identified by SMQs in up to 7 days post-injection, up to 28 days post-injection, and up to EoS will be summarized by SMQ, subordinate SMQ, and PT. Two sets of summary tables will be provided, one will be based on combined broad and narrow scope of SMQ, the other will be based on narrow scope. SMQ and subordinate SMQ within each SMQ will be displayed in alphabetic order. PT will be displayed in descending order of number of participants in mRNA-1345 ([CCI] µg) + Afluria Quadrivalent group and then alphabetically within subordinate SMQ or SMQ if no subordinate SMQ. Detail information for the selected SMQ is presented in Appendix J Table 15 and Table 16.

2.5.3.2.1. Overview of TEAEs

Overall summary of unsolicited TEAEs up to 7 days post-injection, between 8 to 28 days post-injection, and up to 28 days post-injection will be provided, for the number and percentage of participants, along with the number of events, by vaccination group who experience at least one of the categories:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs
- Any unsolicited TEAEs leading to study discontinuation
- Any unsolicited severe TEAEs
- Any unsolicited non-serious TEAEs (no SAE)

- Any unsolicited non-serious severe TEAEs (no SAE)
- Any unsolicited non-serious TEAEs (regardless of SAE)
- Any unsolicited non-serious severe TEAEs (regardless of SAE)
- Any unsolicited AESI

Note: Severe TEAEs include both unsolicited severe TEAEs and ≥ Grade 3 solicited ARs that meet SAE criteria after injection.

Summary tables will also be provided to include number and percentage of participants with unsolicited treatment-related TEAEs up to 28 days post-injection. Additionally, the overall summary for the categories of SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be provided for these TEAEs throughout the study. Separate listings containing individual participant AE data up to EoS for unsolicited TEAEs, serious TEAEs, unsolicited medically-attended TEAEs, unsolicited AESIs, unsolicited TEAEs leading to study discontinuation, severe TEAEs, fatal unsolicited TEAEs, and unsolicited AESIs will be provided.

2.5.3.2.2. TEAEs by System Organ Class and Preferred Term

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

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited non-serious TEAEs
- All unsolicited non-serious severe TEAEs
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related
- All unsolicited TEAEs leading to study discontinuation
- All unsolicited severe TEAEs
- All unsolicited severe TEAEs that are treatment-related
- All unsolicited treatment emergent AESI

Note: Severe TEAEs include both unsolicited severe TEAEs and ≥ Grade 3 solicited ARs that meet SAE criteria after injection.

Summary tables will also be provided for number and percentage of participants with unsolicited TEAEs up to 7 days post-injection, between 8 to 28 days post-injection, and up to 28 days post-injection, and be presented by SOC and PT.

Additionally, summary tables of SAEs, treatment-related SAEs, MAAEs, treatment-related MAAEs, TEAEs leading to study discontinuation, AESIs, and TEAEs leading to death will be also provided by SOC and PT considering all events reported throughout the study. Number of events and number of participants will also be summarized by SOC and PT for participants with AESI up to 7 days post-injection, up to 28 days post-injection, and throughout the study.

2.5.3.2.3. TEAEs by Preferred Term

A summary table for all unsolicited TEAEs up to 28 days after injection will be provided by PT in descending order of frequency in the mRNA-1345 ([CCI] µg) + Afluria Quadrivalent group.

2.5.3.2.4. TEAEs by Severity

The following summary tables of TEAEs up to 28 days after injection will be provided by the severity, SOC and PT using frequency counts and percentages:

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

Summary tables of unsolicited TEAEs up to 28 days after injection with occurrence in ≥ 1% of participants in any vaccination group based on preferred term will be also provided by severity, SOC and PT.

2.5.3.2.5. TEAEs by System Organ Class, High Level Group Term, and Preferred Term

Certain TEAEs, as indicated in Appendix K, will also be summarized by SOC, HLGT, and PT for each vaccination group and presented by three time periods: up to 7 days post-injection, up to 28 days post-injection, and up to EoS after post-injection.

2.5.3.2.6. Independent Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in Section 3.7.6 of the protocol) and provide the assessment to the Sponsor. The CEAC members will be blinded to study

treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review 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.

2.5.3.2.7. Subgroup Analysis of TEAEs

The overview of TEAEs, TEAEs by SOC/PT, TEAEs by Severity, unsolicited treatment-related TEAEs by SOC/PT and serious TEAEs by SOC/PT may be provided for the following subgroup:

- Age group (50 to 59 years, 60 to 74 years, ≥ 75 years)
- Age group (50 to 59 years, ≥ 60 years)
- Sex (male, female)
- Race (White, Black, Asian, other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races])

These summaries may be provided for additional subgroups of selected baseline characteristics.

2.5.3.3. Vital Sign Measurements

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 study visits only in conjunction with a symptom-directed physical examination.

Vital sign measurements, including systolic and diastolic blood pressures, pulse, respiratory rate and body temperature will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing.

Observed pre-injection and post-injection values and change from pre-injection to post-injection at Day 1 will be summarized by vaccination group. Shift from pre-injection to post-injection in the toxicity grades will also be summarized by vaccination group.

The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a participant has a vital sign result with Grade 2 or higher abnormality after injection visit, then all results of that specific vital sign for that participant will be presented in the listing.

2.5.4. Immunogenicity Analysis

The analyses of immunogenicity will be using the PP Set, by vaccination group. The supportive analyses of immunogenicity especially for primary immune response will be conducted using the FAS based on Appendix I. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, additional supportive analyses of non-primary immunogenicity may be conducted using the FAS.

The GMT, GMC, and GM level will be calculated using the following formula:

$$10^{\left\{\frac{1}{n}\sum_{i=1}^{n}\log_{10}(y_{it})\right\}}$$

where $y_{1t}, y_{2t}, \cdots, y_{nt}$ are *n* observed immunogenicity titers or levels for participants *i=1, 2, …, n* at time point *t*.

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

$$10^{\left\{\frac{1}{n}\sum_{i=1}^{n}\log_{10}\left(\frac{y_{it}}{y_{i0}}\right)\right\}} = 10^{\left\{\frac{1}{n}\sum_{i=1}^{n}[\log_{10}(y_{it})-\log_{10}(y_{i0})]\right\}}$$

where $y_{1t}, y_{2t}, \cdots, y_{nt}$ are observed immunogenicity titers or levels for participants i's at time point t. and $y_{10}, y_{20}, \cdots, y_{n0}$ are immunogenicity titers or levels for participants i's at time point 0 (baseline).

2.5.4.1. Immunogenicity Assessments

Immunogenicity assessments will include the following:

- Serum RSV-A neutralizing and RSV-B neutralizing antibody levels
- Serum Anti-HA antibody levels for influenza measured by HAI assay

RSV binding antibody levels may be presented as appropriate.

2.5.4.2. Analysis of the Primary Immunogenicity Endpoints

The co-primary endpoints will be analyzed on the PP Set in order to estimate Estimands 1a-3a (refer to Appendix I, Table 9). In addition, this will be supported by estimation of a treatment policy Estimand (Estimands 1b-3b) on the FAS Set, and by a principal stratum Estimand (Esimands 1c and 2c) on the Supportive PP Set.

2.5.4.2.1. Primary Analysis Approach

The co-primary endpoints include the following:

- GMT of serum RSV-A nAbs at Day 29
- SRR of serum RSV-A nAbs at Day 29
- GMT of serum influenza anti-HA Abs for each influenza strain (A/Victoria, A/Cambodia, B/Victoria, B/Phuket) at Day 29

The statistical analyses are:

- For the co-primary endpoints 1) and 3), the GMT ratio (GMR) between coadministered group and mRNA-1345 plus placebo group or between coadministered group and Afluria Quadrivalent plus placebo group will be estimated using an ANCOVA model on the log-transformed tiers at Day 29, with the vaccination group as the fixed variable, log-transformed baseline titers as a fixed covariate, adjusted for randomized age group. The GLSM for each vaccination group and its corresponding 95% CI in a log-transformed scale will be estimated from the model and back-transformed to obtain the estimates in the original scale as an estimate of the GMT and its 95%CI. The GMR will be estimated by the ratio of the GLSMs and the corresponding 2-sided 95% CI to assess the treatment difference. The noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is > 0.667 based on the noninferiority margin of 1.5.
- For the primary endpoint 2), SRR for RSV-A nAbs at Day 29 will be provided with 2-sided 95% Cis using the Clopper-Pearson method. The SRR difference between coadministered group and mRNA-1345 plus placebo group at Day 29 will be provided with 2-sided 95% Cis using the Miettinen-Nurminen's method. The noninferiority of the SRR will be demonstrated if the LB of the 95% CI of the SRR difference is > -10% based on the noninferiority margin of 10%.

The study is considered to meet the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1345 coadministered with Afluria Quadrivalent based all the co-primary endpoints.

The above analysis corresponds to the Primary Immune Estimands 1a-3a as described in Appendix I, Table 9.

2.5.4.2.2. Sensitivity Analysis

Analyses of the primary endpoints will be performed based on the FAS, using the same method and same definition as described in Section 2.5.4.2.1.

This sensitivity analysis corresponds to the Supportive Immune Estimands 1b-3b as described in Appendix I, Table 9.

2.5.4.2.3. Supportive Analysis

A supportive analysis will be conducted to mitigate the potential power reduction due to the IRT error described in Section 2.3.4. The primary immunogenicity endpoints of GMT and SRR, based on serum RSV-A nAbs at Day 29, will be analyzed on the Supportive PP Set.

The definition of Supportive PP Set can be found in Section 2.4.3. It is estimated that approximately 180 participants in the Per-protocol Immunogenicity Set from mRNA-1345-P301 will be included, along with Group 1 and Group 2 participants in Per-protocol Set from mRNA-1345-P302 to form the Supportive PP Set. The participants from mRNA-1345-P301 and the Group 1 participants from mRNA-1345-P302 will be pooled together and compared with the Group 2 participants from mRNA-1345-P302.

This supportive analysis will be conducted when Part A database is locked and the immunogenicity data for participants in the Supportive PP Set is available. The corresponding Estimand is 1c as described in Appendix I, Table 9. The same definition for the endpoints and the same statistical methods as described in Section 2.5.4.2.1 will be applied in this supportive analysis.

2.5.4.3. Analysis of the Key Secondary Immunogenicity Endpoints

The key secondary endpoints include the following:

1) GMT of serum RSV-B nAbs at Day 29
2) SRR in serum RSV-B nAbs at Day 29
3) SCR in serum influenza anti-HA Abs for each influenza strain (A/Victoria, A/Cambodia, B/Victoria, B/Phuket) at Day 29

The statistical analyses are:

- GMT of RSV-B nAbs at Day 29 will be analyzed using the same ANCOVA model as for RSV-A nAbs at Day 29. The GLSM for each vaccination group and GMR between coadministered group and mRNA-1345 plus placebo group and associated 95% CIs will be estimated from the ANCOVA model.
- SRR in RSV-B nAbs at Day 29 will be provided with 2-sided 95% CIs using the Clopper-Pearson method. The SRR difference between coadministered group and mRNA-1345 plus placebo group at Day 29 will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method.
- SCR in anti-HA Abs for each influenza strain at Days 29 will be provided with 2-sided 95% CIs using the Clopper-Pearson method. The SCR difference between coadministered

group and Afluria Quadrivalent plus placebo group at Day 29 will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method.

The key secondary endpoints of GMT and SRR, based on serum RSV-B nAbs at Day 29, will also be analyzed on the Supportive PP Set.

2.5.4.4. Analysis of Other Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints include the following:

- GMT and GMFR of post-injection/baseline titers to RSV-A nAbs up to Day 181/EoS
- GMT and GMFR of post-injection/baseline titers to RSV-B nAbs up to Day 181/EoS
- SRR and proportion of participants with ≥ 2-fold increases in RSV-A nAb titers up to Day 181/EoS
- SRR and proportion of participants with ≥ 2-fold increases in RSV-B nAb titers up to Day 181/EoS.
- SCR and proportion of participants with ≥ 2-fold increases in influenza anti-HA Abs for each influenza strain at Day 181/EoS
- GMT and GMFR of influenza anti-HA Abs for each influenza strain up to Day 181/EoS

The statistical analyses are:

- GMT of RSV-A nAbs, RSV-B nAbs, and influenza anti-HA Abs for each influenza strain with corresponding 95% CI will be provided at Baseline (Day 1), Day 29, and Day 181/EoS by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at Baseline (Day 1), Day 29, and Day 181/EoS: the number of participants (n), median, minimum and maximum. GMT with 95% CI will be plotted at Baseline (Day 1) and Day 29 by vaccination group.
- GMFR of RSV-A nAbs, RSV-B nAbs, and influenza anti-HA Abs for each influenza strain with corresponding 95% CI will be provided at Day 29 and Day 181/EoS over pre-injection at Day 1 [baseline] by vaccination group. The 95% CIs will be calculated based on the t-distribution of the difference in the log-transformed values (post-baseline time point – Day 1) and then back transformed to the original scale for presentation. GMFR with 95% CI will be plotted at Day 29 by vaccination group.

- Proportion of participants with ≥ 2-fold increases from Day 1 (baseline) in RSV-A nAb titers, RSV-B nAb titers, and influenza anti-HA Abs for each influenza strain at Day 29 and Day 181/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.
- SRR in RSV-A nAb titers and RSV-B nAb titers and SCR in influenza anti-HA Abs for each influenza strain at Day 181/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.

2.5.4.5. Analysis of Exploratory Immunogenicity Endpoints

The exploratory immunogenicity endpoints include the following:

- GMC and GMFR of post-injection/baseline concentration to RSV bAbs up to Day 181/EoS
- Proportions of participants with ≥ 2-fold and ≥ 4-fold increases in RSV bAb concentration up to Day 181/EoS

The following analyses may be performed:

- The analyses of GMC and GMFR of RSV bAbs will be conducted in the same way as the analyses of GMT and GMFR described in Section 2.5.4.4.
- The analyses of proportions of participants with ≥ 2-fold and ≥ 4-fold increases in RSV bAb concentration will be conducted in the same way as the analyses of proportions described in Section 2.5.4.4.

Similar definition and analysis as SRR of RSV nAbs may also be applied on SRR of RSV bAbs.

2.5.4.6. Subgroup Analysis

All the above specified immunogenicity analyses may be performed by the following subgroup as applicable:

- Age groups: 50 to 59 years, 60 to 64 years, ≥ 75 years
- Age group (50 to 59 years, ≥ 60 years)
- Sex (male, female)

2.5.5. Multiplicity Adjustment

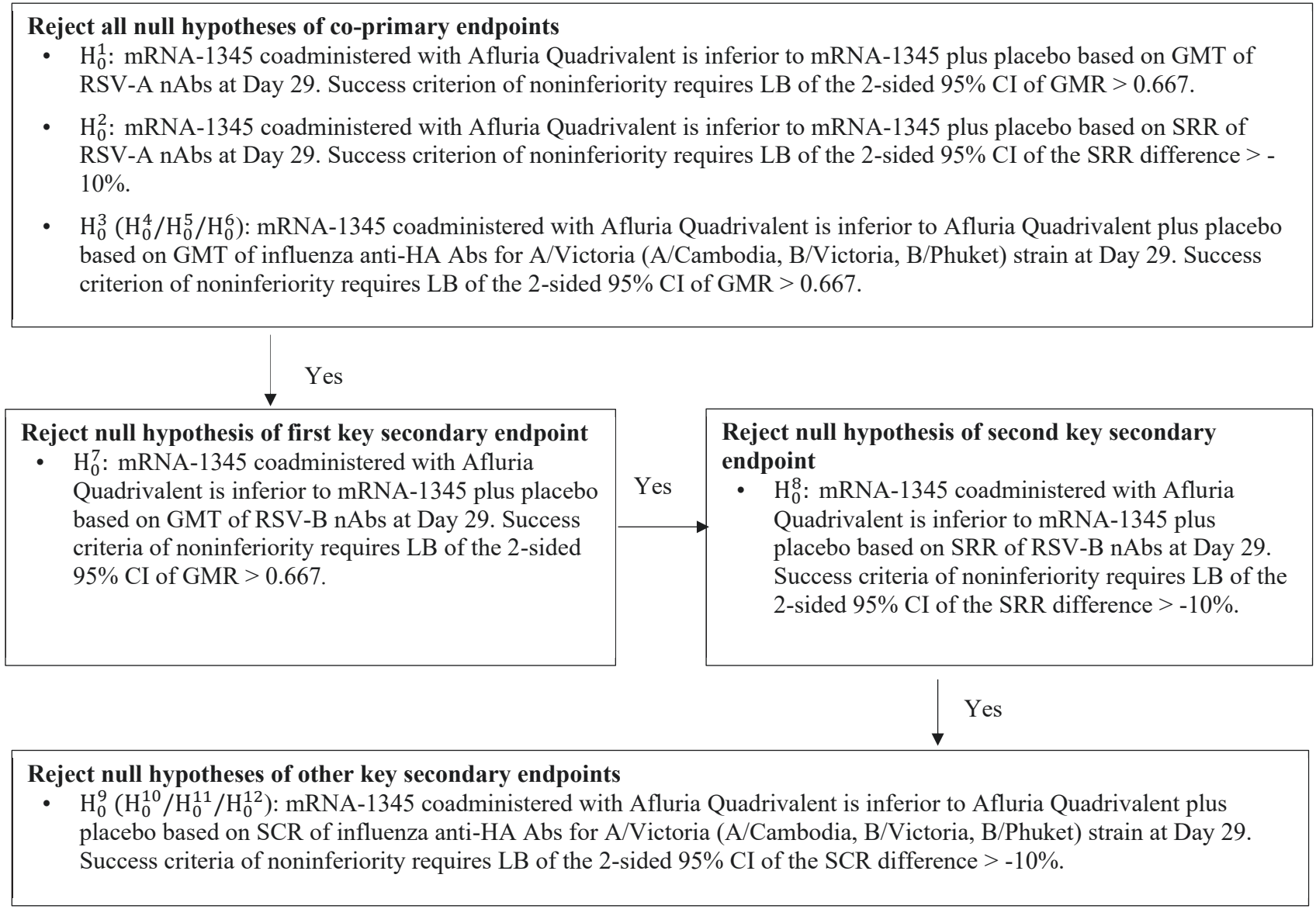
A sequential/hierarchical testing procedure will be used to control the overall Type 1 error rate at 0.05 (2-sided) over the primary endpoints, key secondary efficacy endpoints, and selected secondary endpoint. The hierarchical order for the hypotheses to be tested is indicated in Figure 1 .

The co-primary endpoints will be tested at the planned primary analysis at a 2-sided Type 1 error rate of 0.05. The success criteria of all 6 co-primary endpoints need to be met in order to declare the study a success to achieve noninferiority of coadministration.

The key secondary endpoints will only be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all co-primary endpoints have met success criteria of noninferiority. And the key secondary endpoints will be tested sequentially by GMR of RSV-B nAbs first, SRR of RSV-B nAbs second, then SCR of anti-HA Abs for each influenza strain last.

No further testing will be performed once the sequence/hierarch breaks, that is, further testing stops as soon as an endpoint in the sequence fails to meet success criterion of noninferiority. Analyses of remaining other secondary immune endpoints are not controlled for multiplicity.

Figure 1 Testing Strategy of Co-primary and Key Secondary Immunogenicity Endpoints



2.5.6. Planned Analyses

The following analyses will be conducted on cleaned data:

1. The primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 29 visit.
2. The final analysis of all endpoints will be performed after all participants have completed Day 181/EoS. Results of this analysis will be presented in a final CSR. The final CSR will include full analyses of all safety and immunogenicity data through Day 181/EoS.

In addition, the DSMB will review unblinded primary analysis outputs to safeguard the interests of clinical study participants and to help ensure the integrity of the study. Unblinded data presentation or analysis for DSMB review will be handled by the unblinded statistics team from CRO, who are not involved in study design. More details regarding DSMB analysis can be found in the DSMB charter.

3. Part B

3.1. Study Objectives

3.1.1. Primary Objectives

3.1.1.1. Primary Safety Objective

The primary safety objective of the study is to evaluate the safety and tolerability of the mRNA-1345 vaccine coadministered with mRNA-1273.214.

3.1.1.2. Primary Immunogenicity Objective

The primary immunogenicity objectives are:

1) To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-A
2) To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2

3.1.2. Secondary Objectives

3.1.2.1. Key Secondary Immunogenicity Objectives

The key secondary immunogenicity objective is:

- To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-B

3.1.2.2. Other Secondary Immunogenicity Objectives

The other secondary immunogenicity objectives are:

- To evaluate the Ab response to mRNA-1345 with and without mRNA-1273.214
- To evaluate the Ab response to mRNA-1273.214 with and without mRNA-1345

3.1.3. Exploratory Objectives

The exploratory objectives, which may be performed, is as follow:

- To further characterize the immune response across study vaccines

3.2. Study Endpoints

3.2.1. Primary Endpoints

3.2.1.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Numbers and percentages of participants with solicited local and systemic ARs over the 7 days after each injection.
- Numbers and percentages of participant with unsolicited AEs through 28 days after each injection.
- Numbers and percentages of participants with MAAEs, SAEs, AESIs, and AEs leading to withdrawal from Day 1 (baseline) to EoS.

3.2.1.2. Primary Immunogenicity Endpoints

The primary immunogenicity objectives will be evaluated by the following coprimary endpoints:

- GMT of serum RSV-A nAbs at Day 29.
- SRR in RSV-A nAbs at Day 29. Seroresponse for RSV-A nAbs is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2.
- GMC of serum Ab level as measured by neutralization assay for SARS-CoV-2 at Day 29.
- SRR in SARS-CoV-2 nAbs at Day 29. Seroresponse for SARS-CoV-2 nAbs is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2.

3.2.2. Secondary Endpoints

3.2.2.1. Key Secondary Immunogenicity Endpoints

The key secondary immunogenicity objectives will be evaluated by the following endpoints:

- GMT of serum RSV-B nAbs at Day 29.

- SRR in RSV-B nAbs at Day 29. Seroresponse is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2.

3.2.2.2. Other Secondary Immunogenicity Endpoints

The other secondary immunogenicity objectives will be evaluated by the following endpoints:

- GMT and GMFR of post-injection/baseline titers to RSV-A nAbs up to Day 211/EoS.
- GMT and GMFR of post-injection/baseline titers to RSV-B nAbs up to Day 211/EoS.
- SRR and proportion of participants with ≥ 2-fold increases in RSV-A nAb titers up to Day 211/EoS. A ≥ z-fold increase in RSV A nAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2.
- SRR and proportion of participants with ≥ 2-fold increases in RSV-B nAb titers up to Day 211/EoS. A ≥ z-fold increase in RSV-B nAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2.
- GMC and GMFR as measured by neutralization assay for SARS-CoV-2 up to Day 211/EoS.
- SRR and proportion of participants with ≥ 2-fold increases in SARS-CoV-2 nAb up to Day 211/EoS. A ≥ z-fold increase in SARS-CoV-2 nAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2.

3.2.3. Exploratory Endpoints

- GMC and GMFR of post-injection/baseline concentration to RSV bAbs up to EoS.
- Proportions of participants with ≥ 2-fold and ≥ 4-fold increases in RSV bAb concentration up to Day 211/EoS. A ≥ z-fold increase in RSV bAb concentration is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2.
- GMC and GMFR of post-injection/baseline concentration to SARS-CoV-2 binding Abs up to Day211/EoS.
- Proportion of participants with ≥ 2-fold and ≥ 4-fold increases in SARS-CoV-2 binding Ab concentration up to Day 211/EoS. A ≥ z-fold increase in SARS-CoV-2 bAb concentration is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2.
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

3.3. Study Design

3.3.1. Overall Study Design

Part B is a Phase 3, randomized, observer-blind study to evaluate safety, tolerability, and immunogenicity of mRNA-1345, an mRNA vaccine targeting RSV, when given alone or coadministered with mRNA-1273.214 in adults ≥ 50 years of age.

All participants will participate in a Screening period (up to 14 days before Day 1), treatment period (vaccine and/or placebo administration on Day 1 [Baseline] and on Day 29), and a follow-up period (up to 7 months after first vaccination). The SoA is provided in Appendix G.

The study will enroll approximately 1680 medically stable adults ≥ 50 years of age. On Day 1, each participant will receive 2 injections administered IM, one in each arm, in the deltoid muscle. Participants will be randomized as shown in Table 3 to receive either 1) mRNA-1345 (CCI µg) + placebo (0.9% sodium chloride [normal saline]); 2) mRNA-1345 (CCI µg) + mRNA-1273.214 (CCI µg); or 3) mRNA-1273.214 (CCI µg) + placebo. Randomization will be stratified by age (50 to 59 years, 60 to 74 years, and ≥ 75 years). The study will target enrollment of approximately 35% of participants 50 to 59 years of age. On Day 29, participants will receive an additional injection as outlined in Table 3 to allow all study participants to receive an mRNA-1273.214 booster vaccination.

Table 3: Randomized Groups (Part B)

Group Name	Sample Size	Vaccine Administered
Group 4	560	**Day 1**: mRNA-1345 (CCI µg) + placebo in contralateral arms **Day 29**: mRNA-1273.214 (CCI µg)
Group 5	560	**Day 1**: mRNA-1345 (CCI µg) + mRNA-1273.214 (CCI µg) in contralateral arms **Day 29**: placebo
Group 6	560	**Day 1**: mRNA-1273.214 (CCI µg) + placebo in contralateral arms **Day 29**: placebo

Participants will have a total of 10 visits/safety telephone calls. At the dosing visits on Day 1 and Day 29, participants will be instructed how to document and report solicited ARs in a provided eDiary. Solicited ARs will be assessed from the day of injection and the following 6 days, and local solicited ARs will be assessed separately for each injection site. Unsolicited AEs will be

assessed from the days of injection and the following 27 days. SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be assessed from Day 1 through EoS.

Blood sample collection for humoral immunogenicity will occur on Day 1, Day 29, Day 57, Day 181 and Day 211/EoS. The samples will be processed and analyzed as per the Laboratory Manual. The Day 8 visit (Visit 2) and Day 37 (Visit 4) may be either at the study site or a via a telephone call. The study site staff will perform scheduled safety telephone calls to participants on Day 91, Day 121, and Day 151 to collect AEs, MAAEs, AESIs, AEs leading to withdrawal, SAEs, and information about concomitant medications related to those events and receipt of non-study vaccinations.

3.3.2. Statistical Hypothesis

The immunogenicity primary objectives are to evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-A virus and SARS-CoV-2 (Wuhan-Hu-1 and B.1.1.529 strains). There are 6 co-primary endpoints to support the primary objectives.

Primary Objective to Evaluate the Impact on the Immune Response to RSV-A:

Co-primary endpoints based on GMT at Day 29:

The null hypothesis H_0^1: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1, as measured by GMT at Day 29 using RSV-A nAb assay, is inferior compared with that in participants who received mRNA-1345 plus placebo at Day 1. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA-1345 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB > 0.667) using noninferiority margin of 1.5. The GMR is the ratio of the GMT of RSV-A nAbs in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with the GMT of RSV-A nAbs in participants who received mRNA-1345 plus placebo at Day 1.

Co-primary endpoints based on Seroresponse Rate at Day 29:

The null hypothesis H_0^2: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1, as measured by SRR of RSV-A nAbs at Day 29, is inferior compared with that in participants who received mRNA-1345 plus placebo at Day 1. The noninferiority in SRR in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA-1345 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the SRR difference (coadministered group - mRNA-1345 plus placebo) of ruling out -10% (i.e., LB > -10%) using noninferiority margin of 10%.

Primary Objective to Evaluate the Impact on the Immune Response to SARS-CoV-2:

Co-primary endpoints based on GMC at Day 29:

The null hypotheses H_0^3 to H_0^4: immunogenicity response to mRNA-1273.214 in participants who received mRNA-1273.214 coadministered with mRNA-1345 at Day 1, as measured by GMC of nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29, is inferior compared to that in participants who received mRNA-1273.214 plus placebo at Day 1. For each of the 2 SARS-CoV-2 strains, the noninferiority in the GMC in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA-1273.214 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB > 0.667) using noninferiority margin of 1.5. The GMR is the ratio of the GMC of nAbs in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with the GMC of nAbs in participants who received mRNA-1273.214 plus placebo at Day 1.

Coprimary endpoints based on Seroresponse Rate at Day 29:

The null hypothesis H_0^5 to H_0^6: immunogenicity response to mRNA-1273.214 in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1, as measured by SRR of nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29, is inferior compared with that in participants who received mRNA-1273.214 plus placebo at Day 1. The noninferiority in the SRR in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA-1273.214 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out 10% (i.e., LB > -10%) using a noninferiority margin of 10%. The SRR difference in each strain is the SRR of SARS-CoV-2 nAb of the strain in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 minus the SRR of SARS-CoV-2 nAb of the strain in participants who received mRNA-1273.214 plus placebo at Day 1.

Key Secondary Objective to Evaluate the Impact on the Immune Response to RSV-B:

Key secondary endpoint based on GMT at Day 29:

The null hypothesis H_0^7: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1, as measured by GMT at Day 29 using RSV-B nAb assay, is inferior compared with that in participants who received mRNA-1345 plus placebo at Day 1. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA1345 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB > 0.667) using a noninferiority margin of 1.5. The GMR is the

ratio of the GMT of RSV-B nAbs in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with the GMT of RSV- B nAbs in participants who received mRNA-1345 plus placebo at Day 1.

Hypothesis 7 will be assessed once all the primary hypotheses 1 to 6 are demonstrated.

Key secondary endpoint based on SRR at Day 29:

The null hypothesis H_0^8: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1, as measured by SRR of RSV-B nAbs at Day 29, is inferior compared with that in participants who received mRNA-1345 plus placebo at Day 1. The noninferiority in the SRR in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 compared with that of participants who received mRNA-1345 plus placebo at Day 1 will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out -10% (i.e., LB > -10%) using a noninferiority margin of 10%. The SRR difference is the SRR of RSV-B nAb in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 minus the SRR of RSV-B nAb in participants who received mRNA-1345 plus placebo at Day 1.

Hypothesis 8 will be assessed once all the primary hypotheses and the primary and the key secondary hypothesis (i.e., hypotheses 1 to 7) are demonstrated.

The hierarchical order for the hypotheses to be tested is also indicated in Figure 2

3.3.3. Sample Size and Power

The study will plan to randomize approximately 1680 participants, with approximately 560 participants receiving mRNA-1345 plus placebo at Day 1 and receiving mRNA-1273.214 at Day 29 (Group 4), 560 participants receiving mRNA1345 plus mRNA-1273.214 at Day 1 and receiving placebo at Day 29 (Group 5), and 560 participants receiving mRNA-1273.214 plus placebo at Day 1 and receiving placebo at Day 29 (Group 6).

With approximately 560 participants in each group, the study has approximately 94% probability to observe at least 1 participant in the group with an AE at a true 0.5% AE rate.

Sample Size and Power for the primary immunogenicity endpoints:

Assuming approximately 10% of participants are ineligible to be included in the PP Set, there are 504 eligible participants in each group. The overall power considering meeting the primary objectives to evaluate the immune responses to RSV-A and influenza is 90%. Sample size justification for co-primary endpoints is shown in Table 4.

Table 4: Sample Size Justification for the Co-primary Endpoints (Part B)

Primary Endpoint	Number of Evaluable Participants (with 10% ineligible for Per-protocol Set)	α	Standard Deviation	GMR/SRR Assumed	NI Margin	Power
mRNA-1345 Noninferiority (2-sided test)						
Day 29 GMT Coadministration (Group 5) vs mRNA-1345 alone at Day 1 (Group 4)	504 per group	0.05	1.5	GMR = 1	1.5	99%
Day 29 SRR Coadministration (Group 5) vs mRNA-1345 alone at Day 1 (Group 4)	504 per group	0.05		SRR = 0.8 in both groups	10%	97.8%
mRNA-1273.214 NI (2-sided test) for each SARS-CoV-2 strain (Wuhan-Hu-1 and B.1.1.529)						
Day 29 GMC Coadministration (Group 5) vs mRNA-1273.214 alone at Day 1 (Group 6)	504 per group	0.05	1.5	GMR = 1	1.5	99%
Day 29 SRR Coadministration (Group 5) vs mRNA-1273.214 at Day 1 (Group 6)	504 per group	0.05		SRR = 0.8 in both groups	10%	97.8%
Global power to show noninferiority of the coprimary immunogenicity endpoints						90%

- There is at least 99% power to demonstrate the noninferiority of the immune response to RSV-A, as measured by GMT of RSV-A nAb at Day 29 in participants receiving mRNA-1345 plus mRNA-1273.214 at Day 1 compared with that in participants receiving mRNA-1345 plus placebo at Day 1, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The SD of the natural log-transformed level is assumed to be 1.5.
- There is at least 97.8% power to demonstrate the noninferiority of the immune response, as measured by SRR of RSV-A nAbs at Day 29 in participants receiving mRNA-1345 plus mRNA-1273.214 at Day 1 compared with that in participants

receiving mRNA-1345 plus placebo at Day 1, at a 2-sided alpha of 0.05, assuming an SRR of RSV-A nAbs of 80% in both groups (a true SRR difference is 0), and a noninferiority margin of 10%.

- There is at least 99% power to demonstrate the noninferiority of the immune response to SARS-CoV-2, as measured by GMC of nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29 in participants receiving mRNA-1345 plus mRNA-1273.214 at Day 1 compared with that in participants receiving mRNA-1345 plus placebo at Day 1, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The standard deviation of the natural log-transformed level is assumed to be 1.5.
- There is at least 97.8% power to demonstrate the noninferiority of the immune response to SARS-CoV-2, as measured by SRR of nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29 in participants receiving mRNA-1345 plus mRNA-1273.214 at Day 1 compared with that in participants receiving mRNA-1273.214 plus placebo at Day 1, at a 2-sided alpha of 0.05, assuming an SRR of SARS-CoV-2 nAbs of 80% in both groups (a true SRR difference is 0), and a noninferiority margin of 10%.

Sample Size and Power for the key secondary immunogenicity endpoints:

Assuming approximately 10% of participants are ineligible to be included in the PP Set; 504 participants in each group for sample size in key secondary endpoints:

- There is at least 99% power to demonstrate the noninferiority of the immune response to RSV-B, as measured by GMT of RSV-B nAb at Day 29 in participants from Group 5 compared with that from Group 4, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 1. The standard deviation of the natural log-transformed level is assumed to be 1.5.
- There is at least 97.8% power to demonstrate the noninferiority of the immune response, as measured by SRR of RSV-B nAbs at Day 29 in participants from Group 5 compared with that from Group 4, at a 2-sided alpha of 0.05, assuming a SRR of 80% in both groups (a true SRR difference is 0) and a noninferiority margin of 10%.

3.3.4. Randomization

The randomization will be in a blinded manner using a centralized IRT, in accordance with pre-generated randomization schedules. Randomization details is described in Section 3.3.1.

3.3.5. Blinding and Unblinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with certain exceptions, please refer to Section 3.5.2 of the protocol and Data Blinding Plan for details.

Please see Section 2.3.5 for details.

3.4. Analysis Populations

Please see Section 2.4 for details, except of the following:

- Supportive PP Set will not be applicable in Part B.
- PP Set consists of all participants in the FAS who receive the assigned Day 1 study injections according to protocol regardless of Day 29 injection, comply with immunogenicity blood sampling to have a baseline and at least one Day 29 post-injection assessment within the visit window of study day [22, 43], and have no major protocol deviations that impact the immune response.
- Additionally, 2 subsets of the Solicited Safety Set are defined for Day 1 injection and Day 29 injection. Day 1 (Day 29) Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the study injection on Day 1 (Day 29) and have contributed any solicited AR data (eDiary) from the time of study injection on Day 1 (Day 29) through the following 6 days.

3.5. Statistical Analysis

3.5.1. General Considerations

Please see Section 2.5.1 for details. Differences for Part B are listed as the following:

The Schedule of Assessments is provided in Appendix G.

Study day relative to the Day 1 injection will be calculated as below:

a) Study day prior to the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection (resulting in negative study day);

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

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

a) study day prior to the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection;

b) study day on or after the date of the Day 1 injection but before the Day 29 injection (if applicable) will be calculated as: date of assessment/event – date of the Day 1 injection + 1;

c) study day on or after the date of the Day 29 injection will be calculated as: date of assessment/event – date of the Day 29 injection + 1; if study day is on the same day as the Day 29 injection, date and time will be compared with the Day 29 injection date and time. If it is prior to the Day 29 injection, then study day is calculated as bullet point b); if it is after the Day 29 injection or the time is missing or not available then study day is calculated as: date of assessment/event – date of the Day 29 injection + 1.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B Table 6.

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- D1: mRNA-1345 (CCI µg) + placebo and D29: mRNA-1273.214 (CCI µg)
- D1: mRNA-1345 (CCI µg) + mRNA-1273.214 (CCI µg) and D29: placebo
- D1: mRNA-1273.214 (CCI µg) + placebo and D29: placebo

If a subject receives any dose of mRNA-1345 on Day 1, regardless of the vaccination group the subject is randomized to, the subject will be included in the actual vaccination group received (mRNA-1345 (CCI µg) + placebo/ mRNA-1273.214 (CCI µg) or mRNA-1345 (CCI µg) + mRNA-1273.214 (CCI µg)/ placebo) for safety and reactogenicity analyses. Similar logic will be applied for a subject who receives any dose of mRNA-1273.214.

All analyses and data summaries/displays for disposition, demographics and baseline characteristics, safety and immunogenicity will be provided by vaccination group using appropriate analysis population, unless otherwise specified. Local solicited adverse reactions after Day 1 injection will be also summarized by injection content (mRNA-1345, Placebo and mRNA-1273.214).

3.5.2. Background Characteristics

3.5.2.1. Participant Disposition

Please see Section 2.5.2.1 for details. Differences for Part B are listed as the following:

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

- Received Day 1 injection
- Received Day 29 injection
- Completed the study
- Prematurely discontinued the study and the reason for discontinuation

A participant, who has completed the last scheduled procedure on Day 211 (i.e., 7 months after administration of the study injections on Day 1), is considered to have completed the study.

The number and percentage of participants in each of the following disposition categories will be displayed by vaccination group based on the Safety Set:

- Received Day 1 injection
- Received Day 29 injection

3.5.2.2. Demographics and Baseline Characteristics

Please see Section 2.5.2.2 for details.

3.5.2.3. Medical History

Please see Section 2.5.2.3 for details.

3.5.2.4. Prior and Concomitant Medications

Please see Section 2.5.2.4 for details. Differences for Part B are listed as the following:

For the purpose of analysis, a medication taken prior to the Day 1 injection date, regardless of whether the end date is before or after the Day 1 injection date, is defined “prior”; if the medication is taken through 28 days after any injection (Day 1 and Day 29), then it is considered “concomitant”; if the medication is taken after 28 days post any injection, it is a “post” medication. A complete history (at any time prior to informed consent) about prior COVID-19 vaccinations will also be collected and report.

Concomitant medications will be summarized within 28 days post any injection.

3.5.2.5. Concomitant Procedures/Surgeries

Please see Section 2.5.2.5 for details. Differences for Part B are listed as the following:

For the purpose of analysis, a procedure/surgery occurred prior to the Day 1 injection date (including cases where the procedure/surgery date is completely missing) is defined “prior”; if

the procedure/surgery is performed through 28 days after any injection (Day 1 and Day 29), then it is considered "concomitant"; otherwise, it is a "post" procedure/surgery.

Concomitant procedures will be summarized within 28 days post any injection.

3.5.2.6. Study Exposure

Summary of time on study in days will be presented by vaccination group in Safety Set and PP Set for the following:

- Time on study from randomization in days: calculated as date of study discontinuation/completion – date of randomization +1.
- Time on study from Day 1 injection in days: calculated as date of study discontinuation/completion – date of Day 1 injection +1.
- Time on study from Day 29 injection in days: calculated as date of study discontinuation/completion – date of Day 29 injection +1.

Study injection detail as well as participant with dosing error will be also presented in a listing.

3.5.2.7. Significant Protocol Deviations

Please see Section 2.5.2.7 for details.

3.5.2.8. COVID-19 Impact

Please see Section 2.5.2.8 for details.

3.5.3. Safety Analysis

Please refer to Section 2.5.3 for details.

3.5.3.1. Solicited Adverse Reactions

Please see Section 2.5.3.1 for details. Differences for Part B are listed as the following:

Summaries of solicited ARs will be presented separately after Day 1 injection and Day 29 injection. If a solicited AR started within 6 days after Day 1 injection and ended on or after the Day 29 injection, the AR will only be included in the summaries for solicited AR after Day 1.

Refer to Safety Estimand 9a in Appendix I, Table 12.

3.5.3.2. Adverse Events

Please see Section 2.5.3.2 for details. Differences for Part B are listed as the following:

Unsolicited TEAEs will be summarized up to 28 days post each injection (Day 1 and Day 29). Additionally, SAEs, MAAEs, AESIs and AEs leading to study discontinuation will be

summarized considering all events up 7 days after each injection (Day 1 and Day 29), and throughout the study (up to Day 211/EoS).

Refer to Safety Estimand 9b in Appendix I, Table 12.

3.5.3.2.1. Overview of TEAEs

Please see Section 2.5.3.2.1 for details.

3.5.3.2.2. TEAEs by System Organ Class and Preferred Term

Please see Section 2.5.3.2.2 for details.

A summary table of all unsolicited TEAEs leading to discontinuation from study vaccine will also be provided by SOC and PT using frequency counts and percentages.

3.5.3.2.3. TEAEs by Preferred Term

Please see Section 2.5.3.2.3 for details.

3.5.3.2.4. TEAEs by Severity

Please see Section 2.5.3.2.4 for details.

3.5.3.2.5. TEAE by System Organ Class, High Level Group Term, and Preferred Term

Please see Section 2.5.3.2.5 for details.

3.5.3.2.6. Independent Cardiac Event Adjudication Committee

Please see Section 2.5.3.2.6 for details.

3.5.3.2.7. Subgroup Analysis of TEAEs

Please see Section 2.5.3.2.7 for details.

3.5.3.3. Vital Sign Measurements

Vital signs will only be collected at Screening and on the days of injection (Day 1 and Day 29), once before and at least 30 minutes after injection. Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.

Please see Section 2.5.3.3 for the details of vital sign analyses.

3.5.4. Immunogenicity Analysis

The analyses of immunogenicity will be using the PP Set, by vaccination group. The supportive analyses of immunogenicity especially for primary immune response may be conducted using the FAS based on Appendix I. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than

10%, additional supportive analyses of non-primary immunogenicity may be conducted using the FAS.

Please see Section 2.5.4 for calculations of GMT, GMC, and GMFR.

3.5.4.1. Immunogenicity Assessments

Immunogenicity assessments will include the following:

- Serum RSV-A neutralizing and RSV-B neutralizing antibody levels
- Serum SARS-CoV-2 neutralizing antibody levels

RSV binding or SARS CoV-2 binding antibody levels may be presented as appropriate.

3.5.4.2. Analysis of the Primary Immunogenicity Endpoints

The co-primary endpoints will be analyzed on the PP Set in order to estimate Estimands 5a-8a (refer to Appendix I, Table 11). In addition, this will be supported by estimation of a treatment policy estimand (Estimands 5b-8b) on the FAS Set.

3.5.4.2.1. Primary Analysis Approach

The co-primary endpoints include the following:

1) GMT of serum RSV-A nAbs at Day 29
2) SRR in serum RSV-A nAbs at Day 29
3) GMC of serum nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29
4) SRR in serum nAbs for each of the 2 SARS-CoV-2 strains (Wuhan-Hu-1 and B.1.1.529) at Day 29

The statistical analyses are:

- For the co-primary endpoints 1) and 3), the GMR of RSV-A nAbs or the GMR of nAbs for each of the 2 SARS-CoV-2 strains between vaccination groups will be estimated using an ANCOVA model on the log-transformed titers/concentrations at Day 29, with the vaccination group as the fixed variable, log-transformed baseline titers/concentrations as a fixed covariate, adjusted for randomized age group. The GLSM for each vaccination group and its corresponding 95% CI in a log-transformed scale will be estimated from the model and back-transformed to obtain the estimates in the original scale as an estimate of the GMT or GMC and its 95% CI. The GMR will be estimated by the ratio of the GLSMs

and the corresponding 2-sided 95% CI to assess the treatment difference. The noninferiority of the GMT or GMC will be demonstrated if the LB of the 95% CI of the GMR is > 0.667 based on the noninferiority margin of 1.5.

- For the co-primary endpoints 2) and 4), SRR in RSV-A nAbs or SRR in nAbs for each of the 2 SARS-CoV-2 strains at Day 29 will be provided with 2-sided 95% CIs using the Clopper-Pearson method. The SRR difference between vaccination groups at Day 29 will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method. The noninferiority of the SRR in RSV-A nAbs at Day 29 will be demonstrated if the LB of the 95% CI of the SRR difference between mRNA-1345 + mRNA-1273.214/ placebo and mRNA-1345 + placebo/ mRNA-1273.214 groups is > –10%. The noninferiority of the SRR in nAbs for each of the 2 SARS-COV-2 strains at Day 29 will be demonstrated if the LB of the 95% CI of the SRR difference between mRNA-1345 + mRNA-1273.214/ placebo and mRNA-1273.214 + placebo/ placebo groups is > –10%.

The study is considered to meet the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1345 + mRNA-1273.214/ placebo based all the co-primary endpoints.

The above analysis corresponds to the Primary Immune Estimands 5a-8a as described in Appendix I, Table 11.

3.5.4.2.2. Sensitivity Analysis

Analyses of the primary endpoint will be performed based on the FAS using the same method and same definition as described in Section 3.5.4.1.

This sensitivity analysis corresponds to the Supportive Immune Estimands 5b-8b as described in Appendix I, Table 11.

3.5.4.3. Analysis of the Key Secondary Immunogenicity Endpoints

The key secondary endpoints include the following:

1) GMT of serum RSV-B nAbs at Day 29
2) SRR in serum RSV-B nAbs at Day 29

The statistical analyses are:

- GMT of RSV-B nAbs at Day 29 will be analyzed using the same ANCOVA model as for RSV-A nAbs at Day 29. The GLSM for each vaccination group and GMR between mRNA-1345 + mRNA-1273.214/ placebo group and mRNA-1345 + placebo/ mRNA-1273.214 group and associated 95% CIs will be estimated from the ANCOVA model.

- SRR in RSV-B nAbs at Day 29 will be provided with 2-sided 95% CIs using the Clopper-Pearson method. The SRR difference between mRNA-1345 + mRNA-1273.214/ placebo group and mRNA-1345 + placebo/ mRNA-1273.214 group at Day 29 will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method.

3.5.4.4. Analysis of Other Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints include the following:

- GMT and GMFR of post-injection/baseline titers to RSV-A nAbs up to Day 211/EoS
- GMT and GMFR of post-injection/baseline titers to RSV-B nAbs up to Day 211/EoS
- SRR and proportion of participants with ≥ 2-fold increases in RSV-A nAb titers up to Day 211/EoS
- SRR and proportion of participants with ≥ 2-fold increases in RSV-B nAb titers up to Day 211/EoS
- GMC and GMFR of post-injection/baseline concentration to SARS-CoV-2 nAbs up to Day 211/EoS
- SRR and proportion of participants with ≥ 2-fold increases in SARS-CoV-2 nAb up to Day 211/EoS

The statistical analyses are:

- GMT of RSV-A nAbs and RSV-B nAbs and GMC of SARS-CoV-2 nAbs for each SARS-CoV-2 strain (Wuhan-Hu-1 and B.1.1.529) with corresponding 95% CI will be provided at Baseline (Day 1), Day 29, Day 57, Day 181, and Day 211/EoS by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at Baseline (Day 1), Day 29, Day 57, Day 181, and Day 211/EoS: the number of participants (n), median, minimum and maximum. GMT or GMC with 95% CI will be plotted at Baseline (Day 1) and Day 29 by vaccination group. Reverse cumulative distribution function plot may also be provided.
- GMFR of RSV-A nAbs, RSV-B nAbs, and SARS-CoV-2 nAbs for each SARS-CoV-2 strain (Wuhan-Hu-1 and B.1.1.529) with corresponding 95% CI will be provided at Day 29, Day 57, Day 181, and Day 211/EoS over pre-injection at Day 1 [baseline] by vaccination group. The 95% CIs will be calculated based on the t-distribution of the difference in the log-transformed values (post-baseline time point – Day 1) and then back

transformed to the original scale for presentation. GMFR with 95% CI will be plotted at Day 29 by vaccination group.

- Proportion of participants with ≥ 2-fold increases from Day 1 (baseline) in RSV-A nAb titers, RSV-B nAb titers, and SARS-CoV-2 nAbs for each SARS-CoV-2 strain (Wuhan-Hu-1 and B.1.1.529) at Day 29, Day 57, Day 181, and Day 211/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.
- SRR in RSV-A nAb titers, RSV-B nAb titers, and SARS-CoV-2 nAbs for each SARS-CoV-2 strain (Wuhan-Hu-1 and B.1.1.529) at Day 29, Day 57, Day 181, and Day 211/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.

3.5.4.5. Analysis of Exploratory Immunogenicity Endpoints

The exploratory immunogenicity endpoints include the following:

- GMC and GMFR of post-injection/baseline concentration to RSV bAbs up to Day 211/EoS
- Proportions of participants with ≥ 2-fold increases in RSV bAb concentration up to Day 211/EoS
- GMC and GMFR of post-injection/baseline concentration to SARS-CoV-2 bAbs up to EoS
- Proportions of participants with ≥ 2-fold increases in SARS-CoV-2 bAb concentration up to Day 211/EoS
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

The following analyses may be performed:

- The analyses of GMC and GMFR of RSV bAbs and SARS-CoV-2 bAbs will be conducted in the same way as the analyses of GMT and GMFR described in Section 3.5.4.4.
- The analyses of proportions of participants with ≥ 2-fold increases in RSV bAb and SARS-CoV-2 bAbs concentration will be conducted in the same way as the analyses of proportions described in Section 3.5.4.4.

3.5.4.6. Subgroup Analysis

All the above specified immunogenicity analyses may be performed by the following subgroup as applicable:

- Age groups: 50 to 59 years, 60 to 64 years, ≥ 75 years
- Age group (50 to 59 years, ≥ 60 years)
- Sex (male, female)

3.5.5. Multiplicity Adjustment

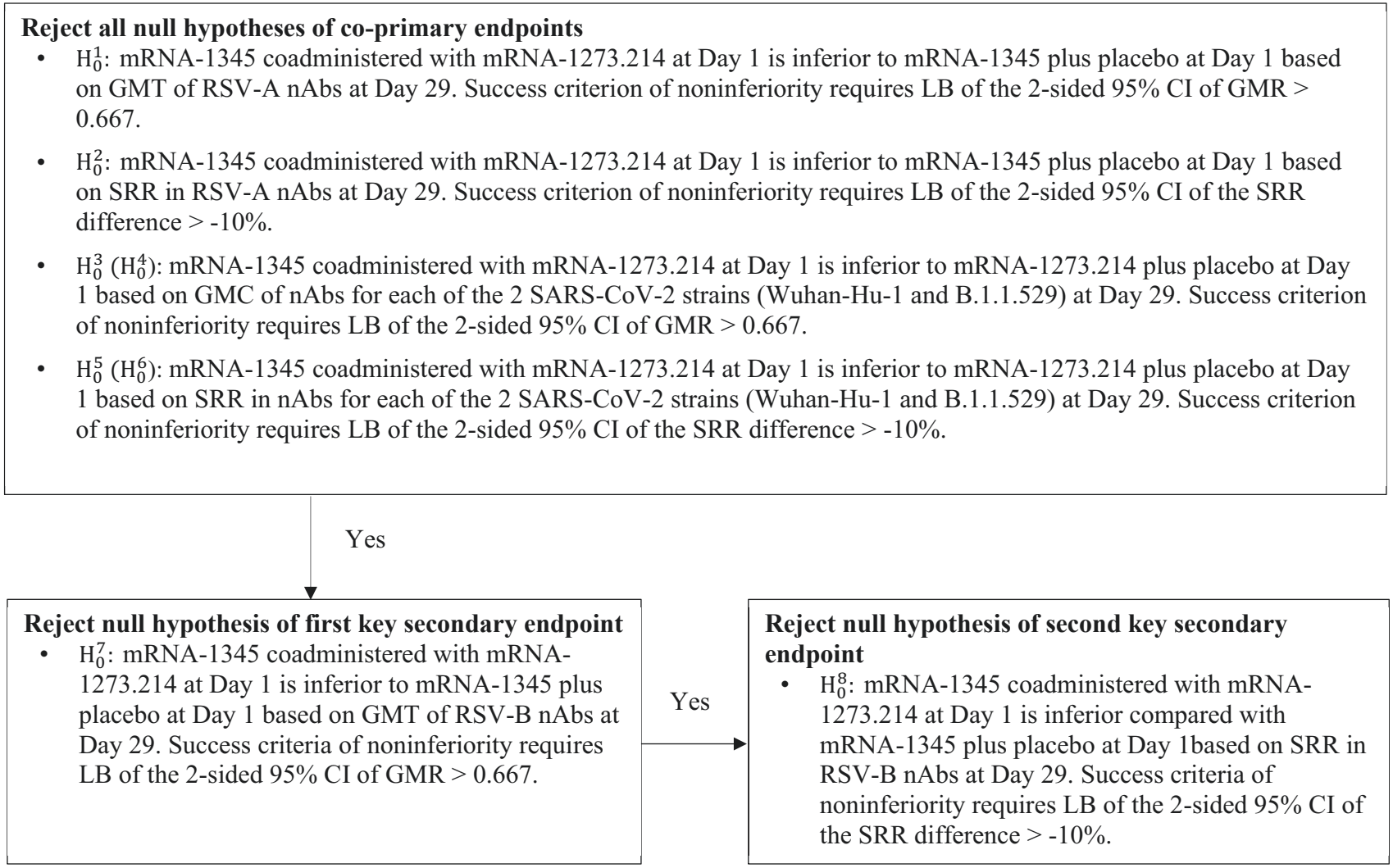
A sequential/hierarchical testing procedure will be used to control the overall Type 1 error rate at 0.05 (2 sided) over the primary endpoints, key secondary efficacy endpoints, and selected secondary endpoint. The hierarchical order for the hypotheses to be tested is indicated in Figure 2.

The co-primary endpoints will be tested at the planned primary analysis at a 2-sided Type 1 error rate of 0.05. The success criteria of all 6 co-primary endpoints need to be met in order to declare the study a success to achieve noninferiority of coadministration.

The key secondary endpoints will only be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all co-primary endpoints have met success criteria of noninferiority. And the key secondary endpoints will be tested sequentially by GMR of RSV-B nAbs first and then SRR of RSV-B nAbs second.

No further testing will be performed once the sequence/hierarch breaks, that is, further testing stops as soon as an endpoint in the sequence fails to meet success criterion of noninferiority. Analyses of remaining other secondary immune endpoints are not controlled for multiplicity.

Figure 2 Testing Strategy of Co-primary and Key Secondary Immunogenicity Endpoints (Part B)



3.5.6. Planned Analyses

The following analyses will be conducted on cleaned data:

1. The primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 29 visit.
2. The final analysis of all endpoints will be performed after all participants have completed Day 211/EoS. Results of this analysis will be presented in a final CSR. The final CSR will include full analyses of all safety and immunogenicity data through Day 211/EoS.

At the primary analysis and other pre-planned analyses, pre-identified Sponsor team members and selected CRO team members as specified in the study data blinding plan will be unblinded to conduct the analyses. More details can be found in the study data blinding plan.

4. Part C

4.1. Study Objectives

4.1.1. Primary Objectives

4.1.1.1. Primary Safety Objective

The primary safety objective of the study is to evaluate the safety and tolerability of a booster dose (BD) of mRNA-1345 administered at 1 Year following a primary dose.

4.1.1.2. Primary Immunogenicity Objective

The primary immunogenicity objectives are:

- To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose
- To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose

4.1.2. Secondary Objectives

4.1.2.1. Secondary Immunogenicity Objectives

The secondary immunogenicity objective is:

- To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 administered at 1 year following a primary dose based on seroresponse
- To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 at all evaluable immunogenicity assessment timepoints

4.1.3. Exploratory Objectives

The exploratory objective, which may be performed, is as follow:

- To further characterize the immune response of a BD of mRNA-1345

4.2. Study Endpoints

4.2.1. Primary Endpoints

4.2.1.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Numbers and percentages of participants with solicited local and systemic ARs through 7 days postBD
- Numbers and percentages of participant with unsolicited AEs through 28 days postBD
- Numbers and percentages of MAAEs from BD Day 1 through BD Day 181
- Numbers and percentages of participants with SAEs, AESIs, and AEs leading to discontinuation from BD Day 1 through BD Day 361/EoS

4.2.1.2. Primary Immunogenicity Endpoints

The primary immunogenicity objectives will be evaluated by the following coprimary endpoints:

- GMT ratio of serum RSV-A nAbs at BD Day 29 over GMT of serum RSV-A-nAbs at Day 29 post primary dose
- GMT ratio of serum RSV-B nAbs at BD Day 29 over GMT of serum RSV-B-nAbs at Day 29 post primary dose

4.2.2. Secondary Endpoints

4.2.2.1. Secondary Immunogenicity Endpoints

The secondary immunogenicity objectives will be evaluated by the following endpoints:

- Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A nAbs at BD Day 29. Seroresponse is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2
- Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B nAbs at BD Day 29. Seroresponse is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2
- GMT and GMFR of postBD/baseline titers to RSV-A nAbs up to BD Day 361/EoS.

- GMT and GMFR of postBD/baseline titers to RSV-B nAbs up to BD Day 361/EoS
- Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A nAbs up to BD Day 361/EoS
- Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B nAbs up to BD Day 361/EoS
- Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-A nAb titers up to BD Day 361/EoS. A ≥ z-fold increase in RSV-A nAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2
- Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-B nAb titers up to BD Day 361/EoS. A ≥ z-fold increase in RSV-A nAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2

4.2.3. Exploratory Endpoints

- GMC and GMFR of postBD/baseline concentration to RSV-bAbs up to BD Day 361/EoS
- Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-bAb concentration up to BD Day 361/EoS. Seroresponse is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.1.2
- Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-bAb concentration up to BD Day 361/EoS. A ≥ z-fold increase in RSV-bAb titers is defined in the same way as for RSV-A nAbs in Part A, Section 2.2.2.2
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

4.3. Study Design

4.3.1. Overall Study Design

Part C is a Phase 3 single arm, open-label, study to evaluate safety, tolerability, and immunogenicity of a BD of mRNA-1345 given at 1 year following a primary dose in adults ≥50 years of age. Participants will be selected from Part B (Groups 4 and 5) of mRNA-1345-P302.

All participants will participate in a Screening period and treatment period according to the timepoints specified in the SoA (Appendix H).

The study will enroll approximately 500 adults ≥50 years of age who are medically stable. On BD Day 1, each participant will receive one IM injection of mRNA-1345 ([CCI] µg), administered into the deltoid muscle of either the right or left arm.

Participants will have a total of 11 scheduled/safety calls. At the dosing visit on BD Day 1, participants will be instructed on how to document and report solicited ARs in a provided eDiary. Local and systemic solicited ARs will be assessed from BD Day 1 through BD Day 7 (the day of injection and the following 6 days). Unsolicited AEs will be assessed from BD Day 1 through BD Day 28 (i.e., the day of injection and the following 27 days). MAAEs will be assessed from BD Day 1 through BD Day 181 (BD Month 6). Serious AEs, Aes leading to discontinuation, and AESIs will be assessed from BD Day 1 through EoS.

Blood sample collection for humoral immunogenicity will occur on BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS. The samples will be processed and analyzed per the Laboratory Manual. The scheduled safety assessment at BD Day 8 may occur either as a study site visit or a telephone call by the study site staff; however, a study site visit is preferred. The study site staff will also perform scheduled safety telephone calls to participants from BD Days 61 to 151 (BD Months 2 to 5), BD Day 241 (BD Month 8), and BD Day 301 (BD Month 10) to collect SAEs, MAAEs, AESIs, Aes leading to discontinuation, and information about concomitant medications related to those events and receipt of nonstudy vaccinations.

Participants may experience AEs that necessitate an unscheduled visit. There may also be situations in which the Investigator asks a participant to attend an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. eCRFs should be completed for each unscheduled visit.

4.3.2. Statistical Hypothesis

The immunogenicity primary objectives are to evaluate the effect of a BD of mRNA-1345 on the immune response to RSV-A and RSV-B virus. There are 2 co-primary endpoints, based on GMT at BD Day 29, to support the primary objectives.

Primary Objective to Evaluate the Impact on the Immune Response to RSV-A:

Co-primary endpoints based on GMT at BD Day 29:

The null hypothesis H_0^1: immunogenicity response to a BD of mRNA-1345, as measured by GMT at BD Day 29 using RSV-A nAb assay, is inferior compared with the GMT at Day 29 post primary dose using RSV-A nAb assay. The noninferiority of the GMT at BD Day 29 will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB>0.667) using a noninferiority margin of 1.5. GMR is the ratio of GMT of RSV-A nAbs at BD Day 29 over GMT of RSV-A nAbs at Day 29 post primary dose, calculated as the back transformation of mean of paired difference of RSV-A nAbs on the logarithmic scale between BD Day 29 and Day 29 post primary dose.

Primary Objective to Evaluate the Impact on the Immune Response to RSV-B:

Co-primary endpoints based on GMT at BD Day 29:

The null hypothesis H_0^2: immunogenicity response to a BD of mRNA-1345, as measured by GMT at BD Day 29 using RSV-B nAb assay, is inferior compared with the GMT at Day 29 post primary dose using RSV-B nAb assay. The noninferiority of the GMT at BD Day 29 will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB>0.667) using a noninferiority margin of 1.5. GMR is the ratio of GMT of RSV-B nAbs at BD Day 29 over GMT of RSV-B nAbs at Day 29 post primary dose, calculated as the back transformation of mean of paired difference of RSV-B nAbs on the logarithmic scale between BD Day 29 and Day 29 post primary dose.

4.3.3. Sample Size and Power

If there are 500 participants, Part C will have approximately 99% and 92% probability to observe at least 1 participant with an AE at a true 1% and 0.5% AE rate, respectively. If there are 450 participants, Part C will have approximately 99% and 90% probability to observe at least 1 participant with an AE at a true 1% and 0.5% AE rate, respectively.

Assuming approximately 10% of participants are ineligible to be included in the Part C PP Set:

- If there are 500 participants, approximately 450 participants will be included in the Part C PP Set.
    - There is approximately 86.6% power to demonstrate the noninferiority of the immunogenicity response in a BD of mRNA-1345 to RSV-A, as measured by GMT of RSV-A nAbs at BD Day 29, compared with the GMT of RSV-A nAbs at Day 29 post primary dose, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5, an underlying GMR of 0.8 (based on the preliminary results in mRNA-1345-P101 study), and the correlation between the titers of RSV-A nAb at BD Day 29 and the titers at Day 29 post primary dose is 0.65. The standard deviation of the natural log-transformed titer level is assumed to be 1.5.
    - There is approximately 98.3% power to demonstrate the noninferiority of the immunogenicity response in a BD of mRNA-1345 to RSV-B, as measured by GMT of RSV-B nAbs at BD Day 29, compared with the GMT of RSV-B nAbs at Day 29 post primary dose, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5, an underlying GMR of 0.85 (based on the preliminary results in mRNA-1345-P101 study), and the correlation between the titers of RSV-B nAb at BD Day 29 and the titers at Day 29 post primary dose is 0.65. The standard deviation of the natural log-transformed titer level is assumed to be 1.5.

  The overall power is approximately 85%.

- If there are 450 participants, approximately 405 participants will be included in the Part C PP Set.
    - There is approximately 82.9% power to demonstrate the noninferiority of the immunogenicity response in a BD of mRNA-1345 to RSV-A, as measured by GMT of RSV-A nAbs at BD Day 29, compared with the GMT of RSV-A nAbs at Day 29 post primary dose, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5, an underlying GMR of 0.8 (based on the preliminary results in mRNA-1345-P101 study), and the correlation between the titers of RSV-A nAb at BD Day 29 and the titers at Day 29 post primary dose is 0.65. The standard deviation of the natural log-transformed titer level is assumed to be 1.5.
    - There is approximately 97.3% power to demonstrate the noninferiority of the immunogenicity response in a BD of mRNA-1345 to RSV-B, as measured by GMT of RSV-B nAbs at BD Day 29, compared with the GMT of RSV-B nAbs at Day 29 post primary dose, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5, an underlying GMR of 0.85 (based on the preliminary results in mRNA-1345-P101 study), and the correlation between the titers of RSV-B nAb at BD Day 29 and the titers at Day 29 post primary dose is 0.65. The standard deviation of the natural log-transformed titer level is assumed to be 1.5.

  The overall power is approximately 80%.

4.3.4. Randomization

Not applicable.

4.3.5. Blinding and Unblinding

Not applicable.

4.4. Analysis Populations

4.4.1. Part C Enrolled Set

The Part C Enrolled Set consists of all participants who complete the informed consent and are not screen failures for Part C.

4.4.2. Part C Per-Protocol Set

The Part C PP set consists of all participants who receive planned BD of mRNA-1345, have a preBD and at least 1 BD Day 29 assessment of immunogenicity within the visit window of study day [22, 43], comply with the immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. The Part C PP Set will be the primary population for the analysis of immunogenicity data.

4.4.3. Part C Safety Set

The Part C Safety Set consists of all participants who receive any BD of mRNA-1345. The Part C Safety Set will be used for the analyses of safety data, except for solicited ARs.

4.4.4. Part C Solicited Safety Set

The Part C Solicited Safety Set consists of all participants who receive BD of mRNA-1345 and contributed any solicited AR data. The Part C Solicited Safety Set will be used for the analyses of solicited ARs.

4.5. Statistical Analysis

4.5.1. General Considerations

Please see Section 2.5.1 for details. Differences for Part C are listed as the following:

The Schedule of Assessments is provided in Appendix H.

Baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the primary dose Day 1 injection, unless otherwise specified. For immunogenicity tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of the primary dose Day 1 injection.

PreBD baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the BD Day 1 injection, unless otherwise specified. For immunogenicity tests, the preBD baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of the BD Day 1 injection.

Study day relative to the primary dose Day 1 injection will be calculated as below:

a) Study day prior to the primary dose Day 1 injection will be calculated as: date of assessment/event – date of the primary dose Day 1 injection (resulting in negative study day);

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

Study day relative to the BD Day 1 injection will be calculated as below:

a) Study day prior to the BD Day 1 injection will be calculated as: date of assessment/event – date of the BD Day 1 injection (resulting in negative study day);

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

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B, Table 7.

Vaccination groups:

Safety and immunogenicity data for Part C will be summarized by the vaccination groups in Part B and overall. The following vaccination groups will be used for summary purposes:

- Part C Booster Dose: mRNA-1345 (CCI µg)
  - Part B Dose D1: mRNA-1345 (CCI ug) + placebo
  - Part B Dose D1: mRNA-1345 (CCI ug) + mRNA-1273.214 (CCI ug)

All analyses and data summaries/displays for disposition, demographics and baseline characteristics, safety, and immunogenicity will be provided by vaccination group in Part B and overall using appropriate analysis population, unless otherwise specified.

For Part C Enrolled Set and Part C Per-Protocol Set, participants will be analyzed or summarized based on the vaccination groups in Part B randomized and overall.

For Part C Safety Set and Part C Solicited Safety Set, participants will be analyzed or summarized based on the vaccination groups in Part B corresponding to the study injection received and overall.

4.5.2. Background Characteristics

4.5.2.1. Participant Disposition

Please see Section 2.5.2.1 for details. Differences for Part C are listed as the following:

The number and percentage of participants in the following categories (analysis sets defined in Section 4.4) will be summarized by vaccination group in Part B and overall as defined in Section 4.5.1 based on Part C Enrolled Set:

- Part C Enrolled Set
- Part C Per-protocol Set
- Part C Safety Set
- Part C Solicited Safety Set

The percentages will be based on the number of participants in the Part C Enrolled Set, except that for the Part C Safety Set and Part C Solicited Safety Set in which the percentages will be based on the number of participants in the Part C Safety Set.

The number and percentage of participants in each of the following disposition categories will be summarized by vaccination group in Part B and overall as defined in Section 4.5.1 based on the Part C Enrolled Set:

- Received BD injection
- Completed the study
- Prematurely discontinued the study and the reason for discontinuation

A participant who has completed the last scheduled procedure on BD Day 361 (i.e., 12 months after administration of the BD) is considered to have completed the study.

4.5.2.2. Demographics and Baseline Characteristics

Please see Section 2.5.2.2 for details. Differences for Part C are listed as the following:

Demographics and baseline characteristics from Part B will be summarized. The summaries will be presented by vaccination group in Part B and overall as defined in Section 4.5.1. The summaries will be presented separately by Part C PP Set and Part C Safety Set.

4.5.2.3. Medical History

Please see Section 2.5.2.3 for details. Differences for Part C are listed as the following:

Medical history prior to Part B will be summarized by vaccination group in Part B and overall as defined in Section 4.5.1 based on the Part C Safety Set. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the overall group and then alphabetically within SOC. Medical history prior to Part B and during the interim period from Part B completion to Part C enrollment will be listed separately based on the Part C Safety Set.

4.5.2.4. Prior and Concomitant Medications

Please see Section 2.5.2.4 for details. Differences for Part C are listed as the following:

Summaries of concomitant medications will be presented by vaccination group in Part B and overall based on the Part C Safety Set.

For the purpose of analysis, a medication taken prior to the BD Day 1 injection date, regardless of whether the end date is before or after the BD Day 1 injection date, is defined “prior”; if the medication is taken through 28 days after the BD injection date (inclusive), then it is considered “concomitant”; if the medication is taken after 28 days post BD injection, it is a “post” medication.

Preferred terms will be displayed in descending order of frequency of the overall group.

4.5.2.5. Concomitant Procedures/Surgeries

Please see Section 2.5.2.5 for details. Differences for Part C are listed as the following:

Summaries of concomitant procedures/surgeries will be presented by vaccination group in Part B and overall based on the Part C Safety Set.

For the purpose of analysis, a procedure/surgery occurred prior to the BD Day 1 injection date (including cases where the procedure/surgery date is completely missing) is defined "prior"; if the procedure/surgery is performed through 28 days after the BD injection date (inclusive), then it is considered "concomitant"; otherwise, it is a "post" procedure/surgery.

SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the overall group and then alphabetically within SOC.

4.5.2.6. Study Exposure

Number and percentage of participants receiving BD injection will be summarized by vaccination group in Part B and overall based on Part C Safety Set and Part C PP Set.

Summary of time on study in days will be also presented by vaccination group in Part B and overall based on Part C Safety Set and Part C PP Set for the following:

- Time on study from primary dose Day 1 injection in days: calculated as date of study discontinuation/completion – date of primary dose Day 1 injection + 1.
- Time on study from BD injection in days: calculated as date of study discontinuation/completion – date of BD Day 1 injection + 1.
- Time from primary dose Day 1 injection to BD injection in days: calculated as date of BD Day 1 injection – date of primary dose Day 1 injection.
- Time from primary dose Day 29 injection to BD injection in days: calculated as date of BD Day 1 injection – date of primary dose Day 29 injection.

Study injection detail will be presented in a listing.

4.5.2.7. Significant Protocol Deviations

Please see Section 2.5.2.7 for details. Differences for Part C are listed as the following:

The number and percentage of the participants with each significant protocol deviation type will be provided by vaccination group in Part B and overall based on the Part C Enrolled Set.

4.5.2.8. COVID-19 Impact

Please see Section 2.5.2.8 for details. Differences for Part C are listed as the following:

An individual data listing on COVID-19 impact will be provided for the Part C Enrolled Set.

4.5.3. Safety Analysis

Please refer to Section 2.5.3 for details. All safety analyses will be based on the Part C Safety Set, except summaries of solicited ARs, which will be based on the Part C Solicited Safety Set. All safety analyses will be provided by vaccination group in Part B and overall as defined in Section 4.5.1, unless otherwise specified.

All safety analyses will be based on safety data collected in Part C, unless otherwise specified.

4.5.3.1. Solicited Adverse Reactions

Please see Section 2.5.3.1 for details.

Refer to Safety Estimand 12a in Appendix I, Table 14.

Additional summaries of Part B solicited adverse reaction data may be performed based on Part C Solicited Safety Set.

4.5.3.2. Adverse Events

Please see Section 2.5.3.2 for details. Differences for Part C are listed as the following:

Unsolicited TEAEs will be summarized up to 28 days post the BD injection. Additionally, MAAEs will be summarized up to 6 months after the BD injection and SAEs, AESIs and AEs leading to study discontinuation will be summarized throughout the study (up to BD Day 361/EoS).

SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the overall group and then alphabetically within SOC.

Refer to Safety Estimand 12b in Appendix I, Table 14.

Additional summaries of Part B AE data may be performed based on Part C Safety Set.

4.5.3.2.1. Overview of TEAEs

Please see Section 2.5.3.2.1 for details. However, overall summary of unsolicited TEAEs between 8 to 28 days post BD injection will not be performed.

4.5.3.2.2. TEAEs by System Organ Class and Preferred Term

Please see Section 2.5.3.2.2 for details. Differences for Part C are listed as the following:

Summary tables of MAAEs will be provided up to 28 days post BD injection and up to 6 months post BD injection.

Summary of unsolicited TEAEs between 8 to 28 days post BD injection will not be performed.

4.5.3.2.3. TEAEs by Preferred Term

Please see Section 2.5.3.2.3 for details.

4.5.3.2.4. TEAEs by Severity

Please see Section 2.5.3.2.4 for details.

4.5.3.2.5. TEAE by System Organ Class, High Level Group Term, and Preferred Term

Please see Section 2.5.3.2.5 for details.

4.5.3.2.6. Independent Cardiac Event Adjudication Committee

Please see Section 2.5.3.2.6 for details.

4.5.3.2.7. Subgroup Analysis of TEAEs

Please see Section 2.5.3.2.7 for details.

4.5.3.3. Vital Sign Measurements

Vital signs will only be collected at Part C Screening and on the day of injection (BD Day 1), once before and at least 30 minutes after injection. Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.

Please see Section 2.5.3.3 for the details of vital sign analyses.

4.5.4. Immunogenicity Analysis

The analyses of immunogenicity will be using the Part C PP Set, by vaccination group in Part B and overall as defined in Section 4.5.1.

Please see Section 2.5.4 for calculations of GMT and GMC, and GMFR.

4.5.4.1. Immunogenicity Assessments

Immunogenicity assessments will include the following:

- Serum RSV-A neutralizing and RSV-B neutralizing antibody levels

RSV binding antibody levels may be presented as appropriate.

4.5.4.2. Analysis of the Primary Immunogenicity Endpoints

The co-primary endpoints will be analyzed on the PP Set in order to estimate Estimands 10a and 11a (refer to Appendix I, Table 13).

4.5.4.2.1. Primary Analysis Approach

The co-primary endpoints include the following:

1) GMT ratio of GMT of RSV-A nAbs at BD Day 29 over GMT of RSV-A-nAbs at Day 29 post primary dose.
2) GMT ratio of GMT of RSV-B nAbs at BD Day 29 over GMT of RSV-B-nAbs at Day 29 post primary dose.

The statistical analyses are:

- For the co-primary endpoints 1) and 2), the GMT ratio (GMR) will be estimated to compare the immune response at BD Day 29 with the response at Day 29 post primary dose. The GMR will be calculated by back transforming the mean of paired difference of nAbs on the logarithmic scale between BD Day 29 and Day 29 post primary dose. The 95% CI for the GMR will be based on t-distribution of the log-transformed values then back transformed to the original scale for presentation. The noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is > 0.667 based on the noninferiority margin of 1.5.

The study is considered to meet the primary immunogenicity objective if the noninferiority of the immune response at BD Day 29 are achieved based the co-primary endpoints.

The above analysis corresponds to the Primary Immune Estimands 10a and 11a as described in Appendix I, Table 13.

4.5.4.3. Analysis of the Secondary Immunogenicity Endpoints

The secondary endpoints include the following:

- SRR from baseline (defined as before primary dose) in RSV-A nAbs at BD Day 29
- SRR from baseline (defined as before primary dose) in RSV-B nAbs at BD Day 29
- GMT and GMFR of post-injection titers over baseline (defined as before primary dose) for RSV-A nAbs up to BD Day 361/EoS
- GMT and GMFR of post-injection titers over baseline (defined as before primary dose) for RSV-B nAbs up to BD Day 361/EoS
- SRR and proportion of participants with ≥ 2-fold increase from baseline (defined as before primary dose) in RSV-A nAb titers up to BD Day 361/EoS
- SRR and proportion of participants with ≥ 2-fold increase from baseline (defined as before primary dose) in RSV-B nAb titers up to BD Day 361/EoS

The statistical analyses are:

- For SRR in RSV-A nAbs and RSV-B nAbs, the difference and 95% CI in the SRR at BD Day 29 versus the SRR at Day 29 post primary dose in the same participants will be estimated through a linear probability model with repeated measure using SAS procedure PROC GENMOD with repeated statement and identity link.

- GMT of RSV-A nAbs and RSV-B nAbs with corresponding 95% CI will be provided at Baseline (primary dose Day 1), primary dose Day 29, primary dose Day 181, BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at Baseline (primary dose Day 1), primary dose Day 29, primary dose Day 181, BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS by vaccination group: the number of participants (n), median, minimum and maximum. GMT with 95% CI at time points post primary dose will be plotted by vaccination group.
- GMFR of RSV-A nAbs and RSV-B nAbs with corresponding 95% CI will be provided at primary dose Day 29, primary dose Day 181, BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS over pre-injection at primary dose Day 1 [baseline] by vaccination group. The 95% CIs will be calculated based on the t-distribution of the difference in the log-transformed values (post-baseline time point – primary dose Day 1) and then back transformed to the original scale for presentation. GMFR with 95% CI at time points post primary dose may be plotted by vaccination group.
- Proportion of participants with ≥ 2-fold increase from primary dose Day 1 (baseline) in RSV-A nAb titers and RSV-B nAb titers at primary dose Day 29, primary dose Day 181, BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.
- SRR in RSV-A nAb titers and RSV-B nAb titers at primary dose Day 29, primary dose Day 181, BD Day 1, BD Day 29, BD Day 181, and BD Day 361/EoS will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.

4.5.4.4. Analysis of Exploratory Immunogenicity Endpoints

The exploratory immunogenicity endpoints include the following:

- GMC and GMFR of post-injection concentration over baseline (defined as before primary dose) for RSV bAbs up to BD Day 361/EoS
- SRR and proportions of participants with ≥ 2-fold increases from baseline (defined as before primary dose) in RSV bAb concentration up to BD Day 361/EoS.

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

The following analyses may be performed:

- The analyses of GMC and GMFR of RSV bAbs will be conducted in the same way as the analyses of GMT and GMFR described in Section 4.5.4.3.
- The analyses of SRR and proportion of participants with ≥ 2-fold increase in RSV bAb concentration will be conducted in the same way as the analyses of proportions described in Section 4.5.4.3.

4.5.4.5. Subgroup Analysis

All the above specified immunogenicity analyses may be performed by the following subgroup as applicable:

- Age groups at enrollment in Part B (50 to 59 years, 60 to 64 years, ≥ 75 years)
- Age groups at enrollment in Part B (50 to 59 years, ≥ 60 years)
- Sex (male, female)
- Race (White, Black, Asian, Other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races]))
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)

4.5.5. Multiplicity Adjustment

The co-primary endpoints will be tested at the planned primary analysis at a 2-sided Type 1 error rate of 0.05. The success criteria of both co-primary endpoints need to be met in order to declare this part of the study a success to achieve noninferiority of a BD.

4.5.6. Planned Analyses

The following analyses will be conducted on cleaned data:

1. The primary analysis of safety and immunogenicity data will be performed after all Part C participants have completed BD Day 29 visit.
2. The final analysis of all endpoints will be performed after all Part C participants have completed BD Day 361/EoS. Results of this analysis will be presented in a final CSR. The final CSR will include full analyses of all safety and immunogenicity data through BD Day 361/EoS.

At the primary analysis and other pre-planned analyses, pre-identified Sponsor team members and selected CRO team members as specified in the study data blinding plan will be unblinded to conduct the analyses. More details can be found in the study data blinding plan.

5. Changes from Planned Analyses in Protocol

The following changes from planned analyses in the study protocol are included in this document:

- Appendix 6.8 Estimands and Estimand Specification: Estimands language has been added for primary immune endpoint and primary safety endpoint.
- Supportive analyses of primary and key secondary immunogenicity endpoints on Supportive PP Set are added in Part A.
- Section 4.4.1 Part C Enrolled Set: Exclude screen failure from Part C Enrolled Set.
- Section 4.5.4.3 Analysis of the Secondary Immunogenicity Endpoints: Methods of calculating 95% CI of paired SRR difference in Part C is updated as linear probability model.

6. References

Donna Spiegelman, Ellen Hertzmark, Easy SAS Calculations for Risk or Prevalence Ratios and Differences, American Journal of Epidemiology, Volume 162, Issue 3, 1 August 2005, Pages 199–200, https://doi.org/10.1093/aje/kwi188.

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985; 4:213-226.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007[cited 2022 Jan 11]. Available from: https://www.fda.gov/media/73679/download.

7. List of Appendices

7.1. Appendix A Standards for Variable Display in TFLs

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

Categorical Variables: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

7.2. Appendix B Analysis Visit Windows

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit or early termination visit, the collected data will be mapped using the analysis visit windows described in Table 5 below for Part A, in Table 6 below for Part B and in Table 7 below for Part C.

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

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

Table 5: Analysis Visit Windows for Immunogenicity Assessments (Part A)

Visit	Visit Window in Study Day
Day 1	1
Day 29	[22, 43]
Day 181	[167, 195]

Table 6: Analysis Visit Windows for Immunogenicity Assessments (Part B)

Visit	Visit Window in Study Day
Day 1	1
Day 29	[22, 43]
Day 57	[50, 71]
Day 181	[167, 195]
Day 211	[197, 225]

Table 7: Analysis Visit Windows for Immunogenicity Assessments (Part C)

Visit	Visit Window in Study Day Relative to the BD Day 1 Injection
BD Day 1	1
BD Day 29	[22, 43]
BD Day 181	[167, 195]
BD Day 361	[347, 375]

7.3. Appendix C Imputation Rules for Missing Dates of Prior/Concomitant Medications

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

1. Missing or partial medication start date:
    - If only Day is missing, use the first day of the month, unless:
    - The medication end date is on/after the date of the injection or is missing/partial AND the start month and year of the medication coincide with the start month and year of the injection. In this case, use the date of the injection.
    - If Day and Month are both missing, use the first day of the year, unless:
    - The medication end date is on/after the date of the injection or is missing/partial AND the start year of the medication coincide with the start year of the IP injection. In this case, use the date of the injection.
    - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication 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.

7.4. Appendix D Imputation Rules for Missing Dates of Procedures/Surgeries

Imputation rules for missing or partial dates of procedures/surgeries are defined below:

- If only Day is missing, use the first day of the month, unless the start month and year of the procedure/surgery coincide with the start month and year of the injection, in this case, use the date of the injection.
- If Day and Month are both missing, use the first day of the year, unless the start year of the procedure/surgery coincide with the start year of the injection, in this case, use the date of the injection.
- If Day, Month, and Year are all missing, the date will not be imputed, but the procedure/surgery will be treated as concomitant.

7.5. Appendix E Imputation Rules for Missing Dates of AEs

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

1. Missing or partial start date:

- If only Day is missing, use the first day of the month, unless:
  - The AE end date is on/after the date of the injection or is missing/partial 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 of the injection.
- If Day and Month are both missing, use the first day of the year, unless:

- The AE end date is on/after the date of the injection or is missing/partial AND the start year of the AE coincides with the start year of the injection. In this case, use the date of the injection.

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

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

7.6. Appendix F Schedule of Events (Part A)

Visit Number	Screening	1	2	3	4, 5, 6, 7	8	USV
Type of Visit	C	C	C/SC	C	SC	C	C
Month Time Point	N/A			M1	M2-M5	M6	Up to M6
Visit Day	Screening[a]	D1 (Baseline)[a]	D8	D29	D57, D91, D121, D151	D181/ EoS	N/A
Window Allowance (Days)	-14	-	+3	-7 to +2	±5	±14	N/A
Informed consent, demographics, concomitant medications[h], and medical history	X	–	–	–	–	–	–
Inclusion/exclusion criteria	X	X	–	–	–	–	–
Physical examination[b]	X	X	–	–	–	–	–
Vital sign measurements[c]	X	X	–	–	–	–	X
Study vaccination (including a 30-minute postdose observation period)[d]	–	X	–	–	–	–	–
Blood sample collection for humoral immunogenicity[e]	–	X	–	X	–	X	–
Pregnancy testing[f]	X	X					
eDiary activation for recording solicited ARs (7 days)[g]	–	X	–	–	–	–	–
Optional blood collection for genomics[e]	–	X	–	–	–	–	–
Optional blood sample for transcriptomics[e]	–	X	–	X	–	X	–
Follow-up safety telephone call[h]	–	–	–	–	X	–	–
Recording of unsolicited AEs	–	X	X	X	–	–	–
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[i]	–	X	X	X	X	X	X
Recording of nonstudy vaccinations[i]	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; D = Day; eDiary = electronic diary; EoS = end of study; M = month; N/A = not applicable; MAAE = medically attended adverse event; SAE = serious adverse event; SC = safety telephone call; USV = unscheduled visit.

[a] The Screening Visit and Day 1 Visit may be performed on the same day or on different days. Additionally, the Screening Visit may be performed over multiple visits if within the 14-day screening window. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time within the 14-day Screening window if they will be eligible upon rescreening.

[b] A full physical examination, including height and weight, will be performed at the Screening Visit. Symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the discretion of the investigator. On the day of study injections, both arms should be examined, and the associated lymph nodes should be evaluated. Any clinically significant findings identified by a healthcare professional during study visits should be reported as an MAAE.

[c] Vital sign measurements include assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). Fever is defined as a body temperature ≥ 38.0 °C/100.4 °F. The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will only be collected at Screening and on the day of vaccination (Day 1), once before and at least 30 minutes after vaccination. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

[d] All participants will be randomized to receive 2 intramuscular injections, one in each arm, in the deltoid muscle.

[e] Blood samples for humoral immunogenicity must be collected prior to administration of the IP on Day 1. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant.

[f] A urine pregnancy test (β-human chorionic gonadotropin) will be performed on all female participants of childbearing potential at Screening and prior to study vaccination on Day 1. A follicle-stimulating hormone (FSH) level may be measured at the discretion of the Investigator to confirm menopausal status. At unscheduled visits, serum or urine pregnancy testing may be performed as needed at the discretion of the Investigator.

[g] The eDiary entries will be recorded by the participant starting approximately 30 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of vaccination and for 6 days following vaccination. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry, but the information entered in the eDiary must come from the participant. Local solicited ARs will be recorded separately for each injection site. See protocol Sections 2.7.1.1 and 2.7.4.3.

[h] Medically qualified study staff will contact all participants. The participant will be interviewed according to the script. Information will be collected about occurrence of unsolicited AEs through 28 days post vaccination, and the occurrence of AESIs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations at all points of contact.

[i] All concomitant medications will be recorded from Day 1 through Day 28 days after vaccination; all nonstudy vaccinations and concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 181/EoS.

7.7. Appendix G Schedule of Events (Part B)

Visit Number	Screening	1	2	3	4	5	6, 7, 8	9	10	USV
Type of Visit	C	C	C/SC	C	C/SC	C	SC	C	C	C
Month Time Point	N/A			M1		M2	M3-M5	M6	M7	Up to M7
Visit Day	Screening[a]	D1 (Baseline)[a]	D8	D29	D37	D57	D91, D121, D151	D181	D211/ EoS	N/A
Window Allowance (Days)	-14	-	+3	-7 + 2	+3	±5	±5	±14	±14	N/A
Informed consent, demographics, concomitant medications, medical history (including COVID), and SARS-Cov-2 vaccination history[h]	X	–	–	–			–	–		–
Inclusion/exclusion criteria	X	X	–	–			–	–		–
Physical examination[b]	X	X	–	–			–	–		–
Vital sign measurements[c]	X	X	–	X			–	–		X
Study vaccination (including a 30-minute postdose observation period)	–	X[d]	–				–	–		–
Day 29 mRNA.214 vaccination or placebo				X						
Blood sample collection for humoral immunogenicity[e]	–	X	–	X		X	–	X	X	–
Pregnancy testing[f]	X	X		X						
eDiary activation for recording solicited ARs (7 days)[g]	–	X	–	X			–	–		–
Optional blood collection for genomics[e]	–	X	–	–			–	–		–
Optional blood sample for transcriptomics[e]	–	X	–	X		X	–	X	X	–
Follow-up safety telephone call[h]	–	–	–	–			X	–		–
Recording of unsolicited AEs (for confirmed cases of RSV or COVID, please see Section 3.7.1	–	X	X	X	X	X	–	–		–

Visit Number	Screening	1	2	3	4	5	6, 7, 8	9	10	USV
Type of Visit	C	C	C/SC	C	C/SC	C	SC	C	C	C
Month Time Point	N/A			M1		M2	M3-M5	M6	M7	Up to M7
Visit Day	Screening[a]	D1 (Baseline)[a]	D8	D29	D37	D57	D91, D121, D151	D181	D211/ EoS	N/A
Window Allowance (Days)	-14	-	+3	-7 + 2	+3	±5	±5	±14	±14	N/A
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[i]	–	X	X	X	X	X	X	X	X	X
Recording of nonstudy vaccinations[i]	X	X	X	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; D = Day; eDiary = electronic diary; EoS = end of study; M = month; mRNA = messenger RNA; N/A = not applicable; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; SAE = serious adverse event; SC = safety telephone call; USV = unscheduled visit.

[a] The Screening Visit and Day 1 Visit may be performed on the same day or on different days. Additionally, the Screening Visit may be performed over multiple visits if within the 14-day Screening window. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time within the 14-day Screening window if they will be eligible upon rescreening.

[b] A full physical examination, including height and weight, will be performed at the Screening Visit. Symptom-directed physical examinations will be performed at other study visits if clinically indicated. Interim physical examinations will be performed at the discretion of the investigator. On the day of study injections, both arms should be examined, and the associated lymph nodes should be evaluated. Any clinically significant findings identified by a healthcare professional during study visits should be reported as an MAAE.

[c] Vital sign measurements include assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). Fever is defined as a body temperature ≥ 38.0 °C/100.4 °F. The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will only be collected at Screening and on the days of vaccination, once before and at least 30 minutes after vaccination. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

[d] All participants will be randomized to receive 2 intramuscular injections, one in each arm, in the deltoid muscle.

[e] Blood samples for humoral immunogenicity must be collected prior to administration of the IP on vaccination days. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant.

[f] A urine pregnancy test (β-human chorionic gonadotropin) will be performed on all women of childbearing potential at Screening and prior to study vaccination. A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm menopausal status. At unscheduled visits, serum or urine pregnancy testing may be performed as needed at the discretion of the investigator.

[g] The eDiary entries will be recorded by the participant starting approximately 30 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of vaccination and for 6 days following vaccination. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry,

but the information entered in the eDiary must come from the participant. Local solicited ARs will be recorded separately for each injection site. See Protocol Section 2.7.1.1 and Protocol Section 2.7.4.3..

[h] Medically qualified study staff will contact all participants. The participant will be interviewed according to the script. Information will be collected about occurrence of unsolicited AEs through 28 days postvaccination and the occurrence of AESIs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations at all points of contact. All concomitant medications will be recorded from the days of vaccination and the following 27 days; all nonstudy vaccinations and concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through EoS. Demographic information relating to the participant's sex, age, and race will be recorded at the Screening visit on the appropriate eCRF page. Medical history of each participant will be obtained by interviewing the participant or by reviewing the participant's medical records and recorded on the Medical History eCRF page. Significant findings that were present prior to the signature of the informed consent will also be included in the Medical History eCRF page.

7.8. Appendix H Schedule of Events (Part C)

Visit Number	Screening	1	2	3	4, 5, 6, 7	8	9	10	11	USV
Type of Visit	V	V	V[a]/SC	V[a]	SC	V[a]	SC	SC	V[a]	V[a]
Month Timepoint	N/A			BD M1	BD M2, M3, M4, M5	BD M6	BD M8	BD M10	BD M12/EoS	Up to BD M12
Visit Day	Screening[b]	BD D1[b,c]	BD D8	BD D29	BD D61, D91, D121, D151	BD D181	BD D241	BD D301	BD D361	N/A
Window Allowance (Days)	-14	–	+3	±7	±5	±7	±5	±5	±14	N/A
Informed consent, concomitant medications[k] and review of medical history	X	–	–	–	–	–	–	–	–	–
Inclusion/exclusion criteria	X	X	–	–	–	–	–	–	–	–
Physical examination[d]	X	X	–	–	–	–	–	–	–	X
Vital sign measurements[e]	X	X	–	–	–	–	–	–	–	X
IRT registration of participant	–	X	–	–	–	–	–	–	–	–
Study injection (including a 30-minute postdose observation period)[f]	–	X	–	–	–	–	–	–	–	–
Blood sample collection for humoral immunogenicity[g]	–	X	–	X	–	X	–	–	X	–
Optional blood sample for transcriptomics[g]	–	X	–	X	–	X	–	–	X	–
Pregnancy testing[h]	X	X	–	–	–	–	–	–	–	–
eDiary activation for recording solicited ARs (7 days)[i]	–	X	–	–	–	–	–	–	–	–
Follow-up safety telephone call[j]	–	–	–	–	X	–	X	X	–	–
Recording of unsolicited AEs	–	X	X	X	–	–	–	–	–	–

Visit Number	Screening	1	2	3	4, 5, 6, 7	8	9	10	11	USV
Type of Visit	V	V	V[a]/SC	V[a]	SC	V[a]	SC	SC	V[a]	V[a]
Month Timepoint	N/A			BD M1	BD M2, M3, M4, M5	BD M6	BD M8	BD M10	BD M12/EoS	Up to BD M12
Visit Day	Screening[b]	BD D1[b,c]	BD D8	BD D29	BD D61, D91, D121, D151	BD D181	BD D241	BD D301	BD D361	N/A
Window Allowance (Days)	-14	–	+3	±7	±5	±7	±5	±5	±14	N/A
Recording of MAAEs and concomitant medications relevant to or for their treatment[j]	–	X	X	X	X	X	–	–	–	–
Recording of SAEs, AESIs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[j]	–	X	X	X	X	X	X	X	X	X
Recording of nonstudy vaccinations[k]	X	X	X	X	X	X	X	X	X	X
Study completion	–	–	–	–	–	–	–		X	–

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BD=booster dose; D=Day; eDiary=electronic diary; EoS=end of study; FSH=follicle-stimulating hormone; IRT=Interactive Response Technology; M=month; N/A=not applicable; MAAE=medically attended adverse event; RSV=respiratory syncytial virus; SAE=serious adverse event; SC=safety telephone call; USV=unscheduled visit; V=visit.

a. All study visits with the exception of Screening and Visit 1 can take place at the study or mobile site or at the home of the participant, where allowed by local regulations, and upon written Sponsor approval. If a visit cannot be scheduled within the indicated allowable window and/or the participant misses the visit, this is considered a protocol deviation. Subsequent visits should be scheduled at the originally planned number of days after Day 1.

b. The Screening Visit and BD Day 1 Visit may be performed on the same day or on different days. Additionally, the Screening Visit may be performed over multiple visits if within the 14-day screening window. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time within the 14-day Screening window if they will be eligible upon rescreening.

c. BD Day 1 visit should occur at least 12 months (but no later than 15 months) from the first mRNA-1345 administration on Day 1 in Part B.

d. A full physical examination, including height and weight, will be performed at the Screening Visit and BD Day 1. Symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the

discretion of the investigator. On the day of the study injection, both arms should be examined, and the associated lymph nodes should be evaluated. Any clinically significant findings identified by a healthcare professional during study visits should be reported as an MAAE.

e. Vital sign measurements include assessment of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (preferred route is oral). Fever is defined as a body temperature ≥38.0°C/100.4°F. The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will only be collected at Screening, on the day of the study injection (BD Day 1), and once before and at least 30 minutes after study injection. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

f. All participants will receive one intramuscular injection on BD Day 1, in one arm, in the deltoid muscle.

g. Blood samples for humoral immunogenicity must be collected prior to administration of the IP on BD Day 1. Transcriptomic samples will be part of the optional biomarker assessment once consented to by the study participant.

h. A urine pregnancy test (β-human chorionic gonadotropin) will be performed on all participants of childbearing potential at Screening and prior to study injection on BD Day 1. An FSH level may be measured at the discretion of the Investigator to confirm menopausal status. At USVs, serum or urine pregnancy testing may be performed as needed at the discretion of the Investigator.

i. The eDiary entries will be recorded by the participant starting approximately 30 minutes after study injection while at the study site with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, on the day of study injection and for 6 days following study injection. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry, but the information entered in the eDiary must come from the participant. Local solicited ARs will be recorded for the injection site. The study site staff will review eDiary data with participants on BD Day 8 visit (Visit 2). See Sections 4.7.1.1and 2.7.4.3.

j. Medically qualified study staff will contact all participants. The participant will be interviewed according to the script. Information will be collected about occurrence of unsolicited AEs through 28 days postinjection, the occurrence of MAAEs and concomitant medications associated with those events through Day 181 postinjection, and the occurrence of SAEs, AESIs, or AEs leading to study discontinuation and concomitant medications associated with those events, and receipt of any nonstudy vaccinations at all points of contact through Day 361/EoS.

k. All concomitant medications will be recorded on from Screening through 28 days following injection; concomitant medications relevant to or for the treatment of an MAAE will be recorded from BD Day 1 through BD Day 181; all nonstudy vaccinations and concomitant medications relevant to or for the treatment of an SAE, AESI, or AE leading to study discontinuation, will be recorded from BD Day 1 through BD Day 361/EoS.

7.9. Appendix I Estimands and Estimand Specifications

Table 8: Intercurrent Events

Label	Intercurrent Event Type
IcEv1 (early discontinuation or unrelated death)	Early discontinuation from study or unrelated death prior to Day 29, the first post-treatment immunogenicity result available.
IcEv2 (Alternative RSV vaccine, flu vaccine or SARS-CoV-2 vaccine)	Use of alternative RSV vaccine, flu vaccine or SARS-CoV-2 vaccine prior to Day 29.
IcEv3 (Prohibited medications)	Use of prohibited medications deemed to impact on immunogenicity prior to Day 29.

Abbreviation: IcEv: intercurrent event; RSV: respiratory syncytial virus.

Table 9: Summary of Primary Immune Estimands with Rationale for Strategies to Address Intercurrent Events (Part A)

Objective: To evaluate the impact of coadministered influenza vaccine on the immune response to RSV		
Estimand Label	**Primary Immune Estimand 1a (on the PP Set)**	**Supportive Immune Estimand 1b (on the FAS Set)**
Estimand Description	Immune response to RSV measured as GMR of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to RSV measured as GMR of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response** and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Endpoint	GMT of RSV-A neutralizing Ab at Day 29 (see Section 2.5.4.2.1).	As per Estimand 1a.
Treatment Conditions	mRNA-1345 + Afluria Quadrivalent (Test) vs. mRNA-1345 plus placebo (Reference)	As per Estimand 1a.

Population-Level Summary	Immune response to RSV defined as GMR of RSV-A neutralizing Ab using an ANCOVA model on the log-transformed tiers at Day 29, with the vaccination group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers.	As per Estimand 1a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative flu vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered influenza vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative flu or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 1a.
Estimand Label	Supportive Immune Estimand 1c (on the Supportive PP Set)	

Estimand Description	Immune response to RSV measured as GMR of RSV-A nAbs at Day 29 in [1] adults ≥ 50 years old who from mRNA-1345-P302 and receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response, or [2] adults ≥ 60 years old who in Per-protocol Immunogenicity Set from mRNA-1345-P301, receive one injection of mRNA-1345 ([redacted] µg) during April to June of 2022, and in the Phase 3 segment from U.S. sites.	
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	
Endpoint	As per Estimand 1a.	
Treatment Conditions	Test group of mRNA-1345 + Afluria Quadrivalent in mRNA-1345-P302 vs. Reference group of mRNA-1345 plus placebo in mRNA-1345-P302 or mRNA-1345 without placebo in mRNA-1345-P301	
Population-Level Summary	As per Estimand 1a.	
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	
IcEv2 (Alternative flu vaccine)	Principal stratum	
IcEv3 (Prohibited medications)	Principal stratum	
Rationale for Strategies	Besides the rationale for strategies as indicated in Estimand 1a, this estimand also seeks to mitigate the statistical power reduction due to the IRT error occurred.	
Objective: To evaluate the impact of coadministered influenza vaccine on the immune response to RSV based on seroresponse from baseline		
Estimand Label	**Primary Immune Estimand 2a** (on the PP Set)	**Supportive Immune Estimand 2b** (on the FAS Set)

Estimand Description	Immune response to RSV measured as SRR difference of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to RSV measured as SRR difference of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response** and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Endpoint	SRR of RSV-A neutralizing Abs at Day 29 (see Section 2.5.4.2.1).	As per Estimand 2a.
Treatment Conditions	mRNA-1345 + Afluria Quadrivalent (Test) vs. mRNA-1345 plus placebo (Reference)	As per Estimand 2a.
Population-Level Summary	Immune response to RSV defined as SRR difference of RSV-A neutralizing Ab using Miettinen-Nurminen's method.	As per Estimand 2a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative flu vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy

Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered influenza vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative flu or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 2a.
Estimand Label	**Primary Immune Estimand 2c** (on the Supportive PP Set)	
Estimand Description	Immune response to RSV measured as SRR difference of RSV-A neutralizing Ab at Day 29 in [1] adults ≥ 50 years old who from mRNA-1345-P302 and receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response, or [2] adults ≥ 60 years old who in Per-protocol Immunogenicity Set from mRNA-1345-P301, receive one injection of mRNA-1345 ([redacted] µg) during April to June of 2022, and in the Phase 3 segment from U.S. sites.	
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	
Endpoint	As per Estimand 2a.	
Treatment Conditions	Test group of mRNA-1345 + Afluria Quadrivalent in mRNA-1345-P302 vs. Reference group of mRNA-1345 plus placebo in mRNA-1345-P302 or mRNA-1345 without placebo in mRNA-1345-P301	
Population-Level Summary	As per Estimand 2a.	
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	

IcEv2 (Alternative flu vaccine)	Principal stratum	
IcEv3 (Prohibited medications)	Principal stratum	
Rationale for Strategies	Besides the rationale for strategies as indicated in Estimand 1a, this estimand also seeks to mitigate the statistical power reduction due to the IRT error occurred.	
Objective: To evaluate the impact of coadministered influenza vaccine on the immune response to influenza		
Estimand Label	**Primary Immune Estimand 3a** (on the PP Set)	**Supportive Immune Estimand 3b** (on the FAS Set)
Estimand Description	Immune response to seasonal influenza measured as GMR of anti-HA Abs as measured by hemagglutination inhibition (HAI) assay at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to seasonal influenza measured as GMR of anti-HA Abs as measured by HAI assay at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response** and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 anti-HA Ab level as measured by HAI assay.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 anti-HA Ab assessment as measured by HAI assay after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 anti-HA Ab assessment as measured by HAI assay.
Endpoint	GMT of anti-HA Abs by HAI assay at Day 29 (see Section 2.5.4.2.1).	As per Estimand 3a.
Treatment Conditions	mRNA-1345 + Afluria Quadrivalent (Test) vs. Afluria Quadrivalent plus placebo (Reference)	As per Estimand 3a.

Population-Level Summary	Immune response to seasonal influenza defined as GMR anti-HA Abs by HAI assay using an ANCOVA model on the log-transformed tiers at Day 29, with the vaccination group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers.	As per Estimand 3a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative flu vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered influenza vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative flu or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 3a.

Table 10: Summary of Primary Safety Estimands with Rationale for Strategies to Address Intercurrent Events (Part A)

Objective: To evaluate the safety and tolerability of the mRNA-1345 vaccine		
Estimand Label	**Safety Estimand 4a**	**Safety Estimand 4b**
Estimand Description	Proportion of participants who would have at least one solicited local or systemic adverse reaction (AR) up to 7 days post-injection. Occurrence of solicited local or systemic ARs during 7 days following study injection will be considered irrespective of the use of other medications. Similar estimands for local solicited ARs, systemic solicited ARs and specific ARs may be specified.	Proportion of participants who would have at least one unsolicited adverse event (AE) up to 28 days post-injection. Occurrence of unsolicited AEs during 28 days following study injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.
Target Population	Adults aged 50 years or older who receive the IP administration and provide solicited ARs data in the first 7 days post-injection.	Adults aged 50 years or older who receive the IP administration.
Endpoint	Incidence of solicited local or systemic ARs in the 7 days following the IP injection.	Incidence of unsolicited AEs in the 28 days following the IP injection.
Treatment Conditions	mRNA-1345 + Afluria Quadrivalent (Test) mRNA-1345 plus placebo (Reference) Afluria Quadrivalent plus placebo (Reference)	Same as Estimand 4a.
Population-Level Summary	Proportion of participants who would experience solicited local or systemic ARs within 7 days of IP injection.	Proportion of participants who would experience unsolicited AEs within 28 days of IP injection.
Intercurrent Event Strategy		
IcEv2 (Alternative flu vaccine)	Treatment Policy	Treatment Policy
IcEv3 (Prohibited medications)	Treatment Policy	Treatment Policy
Rationale for Strategies	Count all relevant safety events observed, **irrespective of the use of other medications**.	

Table 11: Summary of Primary Immune Estimands with Rationale for Strategies to Address Intercurrent Events (Part B)

Objective: To evaluate the impact of coadministered SARS-CoV-2 vaccine on the immune response to RSV		
Estimand Label	**Primary Immune Estimand 5a (on the PP Set)**	**Supportive Immune Estimand 5b (on the FAS Set)**
Estimand Description	Immune response to RSV measured as GMR of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to RSV measured as GMR of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response** and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Endpoint	GMT of RSV-A neutralizing Ab at Day 29 (see Section 3.5.4.2.1).	As per Estimand 5a.
Treatment Conditions	mRNA-1345 + mRNA-1273.214/ placebo (Test) vs. mRNA-1345 + placebo/ mRNA-1273.214 (Reference)	As per Estimand 5a.

Population-Level Summary	Immune response to RSV defined as GMR of RSV-A neutralizing Ab using an ANCOVA model on the log-transformed tiers at Day 29, with the vaccination group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers.	As per Estimand 5a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative SARS-CoV-2 vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered SARS-CoV-2 vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative SARS-CoV-2 or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 5a.

Objective: To evaluate the impact of coadministered SARS-CoV-2 vaccine on the immune response to RSV based on seroresponse from baseline		
Estimand Label	**Primary Immune Estimand 6a** (on the PP Set)	**Supportive Immune Estimand 6b** (on the FAS Set)
Estimand Description	Immune response to RSV measured as SRR difference of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to RSV measured as SRR difference of RSV-A neutralizing Ab at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response and** complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 RSV-A neutralizing Ab assessment.
Endpoint	SRR of RSV-A neutralizing Abs at Day 29 (see Section 3.5.4.2.1).	As per Estimand 6a.
Treatment Conditions	mRNA-1345 + mRNA-1273.214/ placebo (Test) vs. mRNA-1345 + placebo/ mRNA-1273.214 (Reference)	As per Estimand 6a.
Population-Level Summary	Immune response to RSV defined as SRR difference of RSV-A neutralizing Ab using Miettinen-Nurminen's method.	As per Estimand 6a.
Intercurrent Event Strategy		

IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative SARS-CoV-2 vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered influenza vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative flu or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 6a.
Objective: To evaluate the impact of coadministered SARS-CoV-2 vaccine on the immune response to SARS-CoV-2		
Estimand Label	**Primary Immune Estimand 7a** (on the PP Set)	**Supportive Immune Estimand 7b** (on the FAS Set)
Estimand Description	Immune response to SARS-CoV-2 measured as GMR of SARS-CoV-2 nAbs at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to SARS-CoV-2 measured as GMR of SARS-CoV-2 nAbs at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response and** complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb measurement.

Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb measurement after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb measurement.
Endpoint	GMC of SARS-CoV-2 nAbs at Day 29 (see Section 3.5.4.2.1).	As per Estimand 7a.
Treatment Conditions	mRNA-1345 + mRNA-1273.214/ placebo (Test) vs. mRNA-1273.214 + placebo/ placebo (Reference)	As per Estimand 7a.
Population-Level Summary	Immune response to SARS-CoV-2 defined as GMC SARS-CoV-2 nAbs using an ANCOVA model on the log-transformed tiers at Day 29, with the vaccination group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers.	As per Estimand 7a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative SARS-CoV-2 vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy

Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered SARS-CoV-2 vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative flu or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 7a.
Objective: To evaluate the impact of coadministered SARS-CoV-2 vaccine on the immune response to SARS-CoV-2 based on seroresponse from baseline		
Estimand Label	**Primary Immune Estimand 8a** (on the PP Set)	**Supportive Immune Estimand 8b** (on the FAS Set)
Estimand Description	Immune response to SARS-CoV-2 measured as SRR difference of SARS-CoV-2 nAb at Day 29 in adults ≥ 50 years old who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 assessment without major protocol deviations impacting immune response.	Immune response to SARS-CoV-2measured as SRR difference of SARS-CoV-2 nAb at Day 29 in adults ≥ 50 years old who receive IP administration **irrespective of any major protocol deviations impacting immune response** and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb assessment.
Target Population	Adults aged 50 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged 50 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 Day 29 SARS-CoV-2 nAb assessment.
Endpoint	SRR of SARS-CoV-2 nAbs at Day 29 (see Section 3.5.4.2.1).	As per Estimand 8a.
Treatment Conditions	mRNA-1345 + mRNA-1273.214/ placebo (Test) vs. mRNA-1273.214 + placebo/ placebo (Reference)	As per Estimand 8a.

Population-Level Summary	Immune response to SARS-CoV-2 defined as SRR difference of SARS-CoV-2 nAbs using Miettinen-Nurminen's method.	As per Estimand 8a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (Alternative SARS-CoV-2 vaccine)	Principal stratum	Treatment policy
IcEv3 (Prohibited medications)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact during the coadministered SARS-CoV-2 vaccine in adults aged 50 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e., major protocol deviations affecting immune response, use of the alternative SARS-CoV-2 or RSV vaccine, or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 8a.

Table 12: Summary of Primary Safety Estimands with Rationale for Strategies to Address Intercurrent Events (Part B)

Objective: To evaluate the safety and tolerability of the mRNA-1345 vaccine coadministered with mRNA-1273.214		
Estimand Label	**Safety Estimand 9a**	**Safety Estimand 9b**
Estimand Description	Proportion of participants who would have at least one solicited local or systemic adverse reaction (AR) up to 7 days after each injection. Occurrence of solicited local or systemic ARs during 7 days following study injection will be considered irrespective of the use of other medications. Similar estimands for local solicited ARs, systemic solicited ARs and specific ARs may be specified.	Proportion of participants who would have at least one unsolicited adverse event (AE) up to 28 days after each injection. Occurrence of unsolicited AEs during 28 days following study injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.
Target Population	Adults aged 50 years or older who receive the IP administration and provide solicited ARs data in the first 7 days after each-injection.	Adults aged 50 years or older who receive the IP administration.
Endpoint	Incidence of solicited local or systemic ARs in the 7 days following the IP injection.	Incidence of unsolicited AEs in the 28 days following the IP injection.
Treatment Conditions	mRNA-1345 + mRNA-1273.214/ placebo (Test) mRNA-1345 + placebo/ mRNA-1273.214 (Reference) mRNA-1273.214 + placebo/ placebo (Reference)	Same as Estimand 9a.
Population-Level Summary	Proportion of participants who would experience solicited local or systemic ARs within 7 days of IP injection.	Proportion of participants who would experience unsolicited AEs within 28 days of IP injection.
Intercurrent Event Strategy		
IcEv2 (Alternative SARS-CoV-2 vaccine)	Treatment Policy	Treatment Policy
IcEv3 (Prohibited medications)	Treatment Policy	Treatment Policy
Rationale for Strategies	Count all relevant safety events observed, **irrespective of the use of other medications**.	

Table 13: Summary of Primary Immune Estimands with Rationale for Strategies to Address Intercurrent Events (Part C)

Objective: To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 year following a primary dose.	
Estimand Label	**Primary Immune Estimand 10a (on the PP Set)**
Estimand Description	Immune response to RSV measured as GMT ratio of RSV-A neutralizing Ab at BD Day 29 over GMT of RSV-A neutralizing Abs at Day 29 post primary dose in adults ≥ 50 years old who receive BD administration and complied with immunogenicity blood sampling to have preBD and at least 1 BD Day 29 RSV-A neutralizing Ab assessment without major protocol deviations impacting immune response.
Target Population	Adults aged 50 years or older who receive the assigned BD administration, complied with immunogenicity blood sampling to have preBD and at least 1 BD Day 29 RSV-A neutralizing Ab assessment, and have no major protocol deviations impacting the immune response.
Endpoint	GMT ratio of RSV-A neutralizing Ab at BD Day 29 over GMT of RSV-A neutralizing Abs at Day 29 post primary dose (see Section 4.5.4.2.1).
Treatment Conditions	Part C Booster Dose: mRNA-1345 ([redacted] µg) (Test) Part B Dose D1: mRNA-1345 + placebo (Reference) Part B Dose D1: mRNA-1345 + mRNA-1273.214 (Reference)
Population-Level Summary	Immune response to RSV defined as GMR of RSV-A neutralizing Ab by back transforming the mean of paired difference of neutralizing Abs on the logarithmic scale between BD Day 29 and Day 29 post primary dose.
Intercurrent Event Strategy	
IcEv1 (early discontinuation or unrelated death)	Principal stratum
IcEv2 (Alternative RSV vaccine)	Principal stratum
IcEv3 (Prohibited medications)	Principal stratum

Rationale for Strategies	This estimand seeks to understand immune response in adults aged 50 or older who receive the BD and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.
Objective: To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 year following a primary dose.	
Estimand Label	**Primary Immune Estimand 11a** (on the PP Set)
Estimand Description	Immune response to RSV measured as GMT ratio of RSV-B neutralizing Ab at BD Day 29 over GMT of RSV-B neutralizing Abs at Day 29 post primary dose in adults ≥ 50 years old who receive BD administration and complied with immunogenicity blood sampling to have preBD and at least 1 BD Day 29 RSV-B neutralizing Ab assessment without major protocol deviations impacting immune response.
Target Population	Adults aged 50 years or older who receive the assigned BD administration, complied with immunogenicity blood sampling to have preBD and at least 1 BD Day 29 RSV-B neutralizing Ab assessment, and have no major protocol deviations impacting the immune response.
Endpoint	GMT ratio of RSV-B neutralizing Ab at BD Day 29 over GMT of RSV-B neutralizing Abs at Day 29 post primary dose (see Section 4.5.4.2.1).
Treatment Conditions	Same as Estimand 10a.
Population-Level Summary	Immune response to RSV defined as GMR of RSV-B neutralizing Ab by back transforming the mean of paired difference of neutralizing Abs on the logarithmic scale between BD Day 29 and Day 29 post primary dose.
Intercurrent Event Strategy	
IcEv1 (early discontinuation or unrelated death)	Principal stratum
IcEv2 (Alternative RSV vaccine)	Principal stratum

IcEv3 (Prohibited medications)	Principal stratum
Rationale for Strategies	This estimand seeks to understand immune response in adults aged 50 or older who receive the BD and comply with key protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths and major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.

Table 14: Summary of Primary Safety Estimands with Rationale for Strategies to Address Intercurrent Events (Part C)

Objective: To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 year following a primary dose		
Estimand Label	**Safety Estimand 12a**	**Safety Estimand 12b**
Estimand Description	Proportion of participants who would have at least one solicited local or systemic adverse reaction (AR) up to 7 days after BD injection. Occurrence of solicited local or systemic ARs during 7 days following study injection will be considered irrespective of the use of other medications. Similar estimands for local solicited ARs, systemic solicited ARs and specific ARs may be specified.	Proportion of participants who would have at least one unsolicited adverse event (AE) up to 28 days after BD injection. Occurrence of unsolicited AEs during 28 days following study injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.
Target Population	Adults aged 50 years or older who receive the BD administration and provide solicited ARs data in the first 7 days after each-injection.	Adults aged 50 years or older who receive the BD administration.
Endpoint	Incidence of solicited local or systemic ARs in the 7 days following the BD injection.	Incidence of unsolicited AEs in the 28 days following the BD injection.
Treatment Conditions	Part C Booster Dose: mRNA-1345 ([CCI] µg) Part B Dose D1: mRNA-1345 + placebo Part B Dose D1: mRNA-1345 + mRNA-1273.214	Same as Estimand 12a.
Population-Level Summary	Proportion of participants who would experience solicited local or systemic ARs within 7 days of BD injection.	Proportion of participants who would experience unsolicited AEs within 28 days of BD injection.
Intercurrent Event Strategy		
IcEv3 (Prohibited medications)	Treatment Policy	Treatment Policy
Rationale for Strategies	Count all relevant safety events observed, **irrespective of the use of other medications**.	

7.10. Appendix J Definition of TEAE of Clinical Interest by SMQ

Table 15: TEAE of Clinical Interest by SMQ to be Applied in both Part A and Part B

SMQ	**Broad/Narrow Search**	**SMQ Search Criteria**

Anaphylactic Reaction	Algorithmic approach	Specified PT and algorithmic approach specified in Table 16
Angioedema	Broad/Narrow	Specified PT
Arthritis	Broad/Narrow	Specified PT
Cardiac Arrhythmias	Broad/Narrow	Specified PT
Cardiac Failure	Broad/Narrow	Specified PT
Cardiomyopathy	Broad/Narrow	Specified PT
Central Nervous System Vascular Disorders	Broad/Narrow	Specified PT
Convulsions	Broad/Narrow	Specified PT
Demyelination	Broad/Narrow	Specified PT
Embolic and Thrombotic Events	Broad/Narrow	Specified PT
Guillain-Barré Syndrome	Broad/Narrow	Specified PT
Hearing and Vestibular Disorders	Broad/Narrow	Specified PT
Hematopoietic Cytopenia	Broad/Narrow	Specified PT
Hypersensitivity	Broad/Narrow	Specified PT
Immune-mediated/Autoimmune Disorders	Broad/Narrow	Specified PT
Ischemic Heart Disease	Broad/Narrow	Specified PT
Noninfectious Myocarditis/Pericarditis	Broad/Narrow	Specified PT
Peripheral Neuropathy	Broad/Narrow	Specified PT
Vasculitis	Broad/Narrow	Specified PT

Table 16: Algorithmic Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

- A term from Category A
- 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.

- 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.

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
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
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
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

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
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
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

7.11. Appendix K Medical Conditions or Adverse Events by SOC/HLGT/PT

Table 17: Medical Conditions or Adverse Events to be Presented by SOC/HLGT/PT

SOC	HLGT
Cardiac Disorders	Cardiac arrhythmias
	Cardiac disorders, signs and symptoms, NEC
	Cardiac neoplasms
	Cardiac valve disorders
	Coronary artery disorders
	Endocardial disorders
	Heart failures
	Myocardial disorders
	Pericardial disorders
	Cardiac arrhythmias
Nervous System Disorders	Peripheral neuropathies
	PT: Guillain-Barré Syndrome *
	Demyelinating disorders
	PT: Acute disseminated encephalomyelitis *
	Seizures (incl subtypes)
	Central nervous system infections and inflammations
Immune System Disorders	Allergic conditions
	PT: Anaphylactic reaction *

*Only the PT under the HLGT will be presented.

SIGNATURE PAGE

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