CLINICAL STUDY PROTOCOL

Protocol Title:	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
Protocol Number:	mRNA-1345-P302
Sponsor Name:	ModernaTX, Inc.
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Date of Original Protocol:	01 Feb 2022

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	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
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Protocol accepted and approved by:

See eSignature and date signed on last page of the document

Date

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DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "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" dated 16 Jun 2023 and the most recent version of the Investigator's Brochure (IB).

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

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

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

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document	**Date**
Amendment 5	16 Jun 2023
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Amendment 5, 16 Jun 2023: Current Amendment:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or Specialist Term	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BD	booster dose
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
FAS	full analysis set
FluSurv-NET	Influenza Hospitalization Surveillance Network
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least squares mean
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean titer ratio

Abbreviation or Specialist Term	Definition
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	immunoglobulin
IM	intramuscular
IP	investigational product
IST	Internal Safety Team
IRB	Institutional Review Board
IRT	interactive response technology
LB	lower bound
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NH	Northern Hemisphere
PP	per protocol
RSV	respiratory syncytial virus
RSV-LRTD	respiratory syncytial virus-associated lower respiratory tract disease
S-2P	prefusion stabilized spike glycoprotein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation or Specialist Term	Definition
SH	Southern Hemisphere
SoA	schedule of assessments
SCR	seroconversion rate
SRR	seroresponse rate
ULOQ	upper limit of quantification
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

1. INTRODUCTION

This study is divided into Part A (Section 2), Part B (Section 3), and Part C (Section 4).

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 in adults ≥50 years of age.

Part B utilizes a similar study design to Part A with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (mRNA-1273.214) in place of the seasonal influenza vaccine. The differences in the Part B study design are discussed in Section 3.

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.

1.1. Background and Overview

Lower respiratory tract infections, including pneumonia, represent a substantial burden of illness in older adults. It is estimated that lower respiratory infections caused approximately 1.27 million deaths (95% confidence interval [CI]: 1.15-1.34 million) in older adults across 195 countries in 2015 (Global Burden of Disease 2015).

Respiratory syncytial virus

RSV is a single-stranded, enveloped, RNA virus that belongs to the *Pneumoviridae* family. The fusion glycoprotein of the RSV envelope is a conserved target of protective nAbs for both serotypes of RSV: RSV-A and RSV-B. RSV has been identified as one of the important etiologies of acute respiratory disease in older adults and is increasingly recognized as a major cause of illness in adults with certain comorbidities ("high risk"), including those with chronic lung and heart disease (Falsey et al 2000, Falsey et al 2005, Shi et al2020).

A 4-year prospective cohort study indicated that RSV infection developed annually in 3% to 7% of healthy older adults and in 4% to 10% of high-risk adults, translating to an estimated 177,000 hospital admissions, 14,000 deaths, and hospitalization costs exceeding $1 billion each year in the US (Falsey et al 2005). An active surveillance study across multiple centers in the US estimated that the hospital admission rate of RSV-associated community-acquired pneumonia in adults aged 50 to 64 years was 0.8 cases/10,000 persons per year, with higher rates in adults aged 65 to 79 years (2.5 cases/10,000 persons per year) and ≥80 years (5.0 cases/10,000 persons per year) (Jain et al 2015). Globally, there are an estimated 336,000 hospitalizations (95% CI: 186,000-614,000) and 14,100 in-hospital deaths (95% CI: 4,800-50,500) in older adults each year related to RSV-associated acute respiratory infection (Shi et al 2020).

While most adults have been previously infected with RSV and therefore demonstrate some level of RSV protective immunity, the immune requirements for protection in older adults are not well understood. The level of humoral response is a strong correlate of immune protection, as decreased serum neutralizing activity and/or decreased nasal RSV-specific immunoglobulin (Ig)A are risk factors for RSV infection, including more severe disease (Duncan et al 2009; Falsey et al 2000; Luchsinger et al 2012; Piedra et al 2003; Walsh et al 2013). Waning cellular immunity may also play a role in the susceptibility of the elderly to RSV infections, as healthy adults older than 60 years of age have increased numbers of regulatory (immunosuppressive)

T cells and fewer RSV-specific CD8+ T cells (Cherukuri et al 2013; Cusi et al 2010; de Bree et al 2005; Kurzweil et al 2013; Looney et al 2002).

Therefore, with no existing approved vaccine or specific therapy for RSV infection, RSV remains a significant unmet medical need globally.

Influenza

Influenza is a respiratory virus that has a segmented RNA genome, allowing for new strains to arise by genetic reassortment (Bartoszko et al 2021). Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 million to 5 million cases of severe illness and up to 650,000 deaths each year resulting in a severe challenge to public health (WHO 2018). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the Northern Hemisphere (NH) and Southern Hemisphere (SH) (Riedel et al 2019). Since influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto et al 2018). Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice per year (once for the NH and once for the SH). Influenza A and influenza B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages).

It is well accepted that the risk of complications due to influenza increases with age (Bartoszko et al 2021). An analysis of the US Influenza Hospitalization Surveillance Network (FluSurv-NET) showed that hospitalization rates among adults aged 75–84 years and ≥85 years were 1.4–3.0 and 2.2–6.4 times greater, respectively, than rates for adults aged 65–74 years. In-hospital death or transfer to hospice occurred in 3.8% of patients aged 65–74 years, 5.3% of patients aged 75–84 years, and 8.7% of patients aged ≥85 years (Czaja et al 2019). Similarly, data from 33 countries demonstrated that the highest excess mortality rates were found among patients aged 75 years and older (17.9–223.5 per 100,000) (Iuliano et al 2018).

Respiratory syndrome coronavirus 2 (SARS-CoV-2)

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome. An outbreak of a novel CoV (later designated SARS-CoV-2, the causative agent of coronavirus disease 2019 [COVID-19]) initially emerged in Wuhan, Hubei Province, China in December 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020, and COVID-19 continues to have a major global public health impact, with more than 500 million cases and 6.2 million deaths as of 27 Apr 2022. ModernaTX, Inc. (Sponsor), leveraged its foundational understanding of messenger ribonucleic acid (mRNA) vaccine approaches against CoV to develop a rapid response proprietary vaccine platform and the mRNA-1273 (SPIKEVAX™) vaccine, which is a lipid nanoparticle (LNP) encapsulated, mRNA-based vaccine against SARS-CoV-2.

Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. With the Omicron variant [B.1.1.529] as the predominant variant circulating since November 2021, public health experts have observed cases of breakthrough infection, although most such cases have

been mild to moderate. The US Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control have identified and concurred with the use of booster vaccinations of the prototype vaccine to bridge the gap until a variant-matched vaccine which confers superior protection can be available.

1.1.1. mRNA-1345

ModernaTX, Inc. (the Sponsor) has developed a rapid response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating and transient, and delivers only the elements required for expression of the encoded protein.

mRNA-1345 is a lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine to prevent disease associated with RSV infection.

mRNA-1345 encodes the RSV fusion glycoprotein that is stabilized in the prefusion conformation. The fusion protein exists in 2 primary conformational states, the metastable prefusion state drives fusion of the virus and host cell membranes through a conformational change to the stable postfusion state. The prefusion conformation is the primary target of the natural immune response to RSV, displays all the epitopes known to elicit nAbs, and induces a higher nAb response than the postfusion conformation, both in animal models and humans (Crank et al 2019, Graham 2019, McLellan et al 2013, Ngwuta et al 2015).

1.1.2. Afluria® Quadrivalent Influenza Vaccine

Afluria® Quadrivalent is an egg-based, inactivated influenza vaccine indicated for active immunization against influenza disease. The vaccine will be provided to the study site in its commercial packaging, containing the recommended influenza strains for the 2021-2022 influenza season in the NH.

1.1.3. mRNA-1273.214

mRNA-1273.214 is based on the same platform described in Section 1.1.1. mRNA-1273.214 contains CX-024414, the mRNA that encodes for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2 and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant.

1.1.4. Study Rationale

Part A:

The Sponsor's position is that the coadministration of mRNA-1345 with a seasonal influenza vaccine will allow people to receive both vaccines at once to reduce the number of visits and add to the uptake/convenience in the elderly population that is at risk for both severe RSV and influenza diseases.

Part B:

The Sponsor's position is that the coadministration of mRNA-1345 with vaccines that are recommended for older adults, including SARS-CoV-2 vaccines, will allow people to receive

both vaccines at once to reduce the number of visits and add to the uptake/convenience in the elderly population that is at risk for both severe RSV and COVID.

Part C:

The Sponsor's position is that administering a booster at 1 year following initial mRNA-1345 vaccination will allow for the assessment of whether re-vaccination increases RSV antibody titers to comparable levels observed after initial administration of mRNA-1345.

1.1.5. Nonclinical Studies

Nonclinical immunogenicity and safety studies have been completed by the Sponsor with mRNA-1345 or similar mRNA-based vaccines formulated in SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl) (6 oxo-6-(undecyloxy) hexyl) amino) octanoate), the custom manufactured lipid used in the mRNA-1345 LNP formulation.

In an in vivo dose-response study, the immunogenicity of mRNA-1345 was evaluated in female BALB/c mice at 4 dose levels (CCI [redacted] µg) after intramuscular (IM) injections on Day 1 and Day 22. mRNA-1345 induced a dose-dependent RSV-nAb and bAb response and a balanced Ig G2a:IgG1 response, indicating a T helper 1 response.

In addition, in a non-Good Laboratory Practice immunogenicity and safety study in Sprague Dawley rats, mRNA-1345 was administered at clinically relevant dose levels of CCI [redacted] µg/dose via IM injections on Day 1 and Day 22. Respiratory syncytial virus-nAbs were detected in the serum of all animals administered mRNA-1345, and a dose-dependent nAb response was observed. Administration of mRNA-1345 was well tolerated up to CCI µg/dose. There were no mRNA-1345 –related mortalities or changes in body weight or body weight gains. Clinical signs consisted of transient local effects of edema and impaired limb functions at the injection site. Changes in clinical pathology parameters were consistent with an inflammatory response, in addition to a mild liver effect in individual animals.

A detailed review of nonclinical experience with the mRNA-1345 vaccine is provided in the IB.

For a detailed review of nonclinical experience with the mRNA-1273.214/1273 vaccine, please refer to the most recent version of the mRNA-1273 IB.

1.1.6. Clinical Studies

The mRNA-1345 vaccine is currently being evaluated for safety and immunogenicity in a Phase 1 study (NCT04528719) and a Phase 2/3 study (NCT05127434).

The Phase 1 study (mRNA-1345-P101) is an observer-blind, placebo-controlled, dose-escalation study of mRNA-1345 in healthy younger adults aged 18 to 49 years, women of childbearing potential aged 18 to 40 years, healthy older adults aged 65 to 79 years, Japanese older adults aged ≥60 years, and RSV seropositive children aged 12 to 59 months. Five dose levels of mRNA-1345 are to be evaluated in the Phase 1 study, first CCI µg, CCI µg, and CCI µg dose levels in healthy younger adults aged 18 to 49 years, and then CCI µg, CCI µg, and CCI µg dose levels in women of childbearing potential and CCI µg, CCI µg, CCI µg, CCI µg, and CCI µg dose levels in healthy older adults aged 65 to 79 years (CCI µg dose level in Japanese healthy older adults aged ≥60 years), as well as CCI µg and CCI µg dose levels in RSV seropositive children aged 12 to 59 months. Older adult participants enrolled in the US who initially received mRNA-1345 on

Day 1 will also receive the same dose level of mRNA-1345 or placebo as a BD at Month 12. The results from this initial study will be used to support and inform subsequent evaluations of the mRNA-1345 vaccine in future clinical studies.

The Phase 2/3 study (mRNA-1345-P301) is a randomized, observer-blind, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of mRNA-1345 in adults ≥60 years of age. In Phase 2 part between 400 and 2,000 participants will be randomly assigned to receive a single injection of CCI µg of the mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Enrollment in the Phase 3 part of the study will be triggered by the DSMB's review of the Day 29 safety data from the first 400 participants in the Phase 2 part of the study. In Phase 3, between 32,000 and 33,600 participants will be randomly assigned to receive a single injection of either CCI µg of the mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Overall, approximately 37,000 participants will be enrolled in the Phase 2/3 study.

mRNA-1273 (SPIKEVAX) booster is marketed globally. mRNA-1273.214 is currently under investigation as a single CCI µg booster dose in adults ≥18 years of age who have previously received the mRNA-1273 primary series as well as a booster dose (mRNA-1273-P205). mRNA-1273.214 is also under investigation in a Phase 3 study as a single CCI µg booster dose in adults ≥16 years of age in the UK (mRNA-1273-P305). For a detailed review of clinical experience with the mRNA-1273.214/1273 vaccine, please refer to the most recent version of the mRNA-1273 IB.

1.2. Benefit/Risk Assessment

Summaries of the potential risks and benefits of mRNA-1345 and mRNA-1273 are provided in the most recent versions of the IBs.

1.2.1. Known Potential Benefits

Participants who receive mRNA-1345 may or may not directly benefit from the vaccination, as the efficacy of mRNA-1345 is yet to be established.

Participants will be contributing to the process of developing a new potentially prophylactic measure in an area of unmet medical need (the prevention of RSV-LRTD).

Participants who receive the mRNA-1273.214 vaccine as a booster dose in Part B of the study may be provided with improved protection against COVID-19 variants of concern.

1.2.2. Risks From Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after study injection.

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

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of the vaccination.

Most systemic AE) observed after vaccination do not exceed mild-to-moderate severity. The most commonly reported systemic ARs are anticipated to be fever, fatigue, chills, headache, myalgia, and arthralgia.

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following vaccination were observed in some clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown.

In the post-authorization setting, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases, and individuals tend to recover within a short time following standard treatment and rest. Investigators and participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

1.2.3. Overall Benefit/Risk Conclusion

Appropriate eligibility criteria, as well as specific criteria for delaying the vaccination, are included in this protocol. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study assessments and procedures.

All safety findings will be closely monitored and reviewed by the study team as well as an Internal Safety Team (IST) and an independent DSMB (Part A and Part B) to evaluate the safety and treatment status of all participants. The DSMB will review and assess the safety data as described in a separate charter.

The proposed Phase 3 clinical study (Part A) evaluating the coadministration of mRNA-1345 and Afluria Quadrivalent in adults ≥50 years of age is supported by nonclinical safety and immunogenicity studies and a Phase 1 clinical study.

Considering the measures used to minimize the risk to individuals participating in this study and oversight by the study team, an IST, and independent DSMB (Part A and Part B), the potential risks to the participants are justified by the potential benefits linked to the development of the RSV vaccine and its coadministration with a commercially available influenza vaccine (Part A) or approved/investigational SARS-CoV-2 vaccine (Part B) or as a booster dose at 1 year following a primary dose (Part C).

For participants who receive mRNA-1273.214 (Part B), considering the nonclinical data for mRNA-1273.214 and clinical trial safety data for mRNA-1273 (and other mRNA vaccines manufactured to date by the Sponsor that contain the proprietary SM-102 lipid formulation), the Sponsor considers the potential benefits of participation to exceed the risks.

2. PART A

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** in adults ≥50 years of age.

2.1. Protocol Summary

2.1.1. Synopsis (Part A)

Protocol Title:

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

Regulatory Agency Identifier Numbers:

Investigational New Drug: 23342

Rationale:

This study is designed as a randomized, observer-blind study to evaluate the safety and immunogenicity of mRNA-1345 when coadministered with a commercial influenza vaccine (Afluria Quadrivalent) compared with either vaccine alone in older adults ≥50 years of age who are medically stable. Participants will receive either mRNA-1345 + placebo, mRNA-1345 + Afluria Quadrivalent, or Afluria Quadrivalent + placebo in contralateral arms.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent)	• Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) over the 7 days postinjection • Numbers and percentages of unsolicited adverse events (AEs) through 28 days postinjection • Numbers and percentages of medically attended AEs (MAAEs), serious AEs (SAEs), adverse events of special interest (AESIs) and AEs leading to withdrawal Day 1 (baseline) to Day 181/ EoS
• To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A	• Geometric mean titer (GMT) of serum RSV-A neutralizing Abs at Day 29 • Seroresponse rate (SRR) in RSV-A neutralizing Abs at Day 29

Objectives	Endpoints
• To evaluate the impact of coadministered RSV vaccine on the immune response to influenza	• GMT of serum Ab level as measured by hemagglutination inhibition (HAI) assay for influenza at Day 29
Key Secondary	
• To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-B	• GMT of serum RSV-B neutralizing Abs at Day 29 • SRR in RSV-B neutralizing Abs at Day 29
• To evaluate the impact of coadministered RSV vaccine on the immune response to influenza based on seroconversion from baseline	• Seroconversion rate (SCR) in influenza A and B strains at Day 29
Secondary	
• To evaluate Ab response to mRNA-1345 with and without a seasonal influenza vaccine (Afluria® Quadrivalent)	• GMT and geometric mean fold rise (GMFR) of post-injection/baseline titers to RSV-A neutralizing Abs up to Day 181/EoS • GMT and GMFR of post-injection/baseline titers to RSV-B neutralizing Abs up to Day 181/EoS • Proportion of participants with ≥2-fold increases in RSV-A neutralizing Ab titers up to Day 181/EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-B neutralizing Ab titers up to Day 181/EoS
• To evaluate the Ab response to seasonal influenza vaccine (Afluria® Quadrivalent) with and without mRNA-1345	• SCR at Day 181/EoS in anti-HA Abs measured by HAI assay • GMT and GMFR of serum Ab level as measured by HAI assay for influenza up to Day 181/EoS
Exploratory (may be performed)	
• To further characterize the immune response across study vaccines	• Geometric mean concentration (GMC) and GMFR of post-injection/baseline titers to RSV-binding Abs up to Day 181/EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-binding Ab concentration up to Day 181/EoS

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

Overall Design:

Part A is a Phase 3, randomized, observer-blind study to evaluate the 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 study will enroll approximately 1620 adults ≥50 years of age who are medically stable. 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 the below table 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.

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 electronic diary (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). Serious AEs, 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 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 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. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

Brief Summary:

The purpose of this study is to assess the safety and immune response of mRNA-1345, an mRNA vaccine targeting RSV, when given alone or coadministered with a seasonal influenza vaccine in healthy older adults.

Study details include:

- The study duration will be up to 6 months.
- The treatment is 2 injections on Day 1.
- The visit frequency will be 3 visits in the first month (Days 1 [clinic], 8 [clinic or telephone call], and 29 [clinic]); 4 (one per month) safety telephone calls from Months 2 through 5, and a clinic visit at Month 6.

Number of Participants:

Approximately 1620 participants will be enrolled.

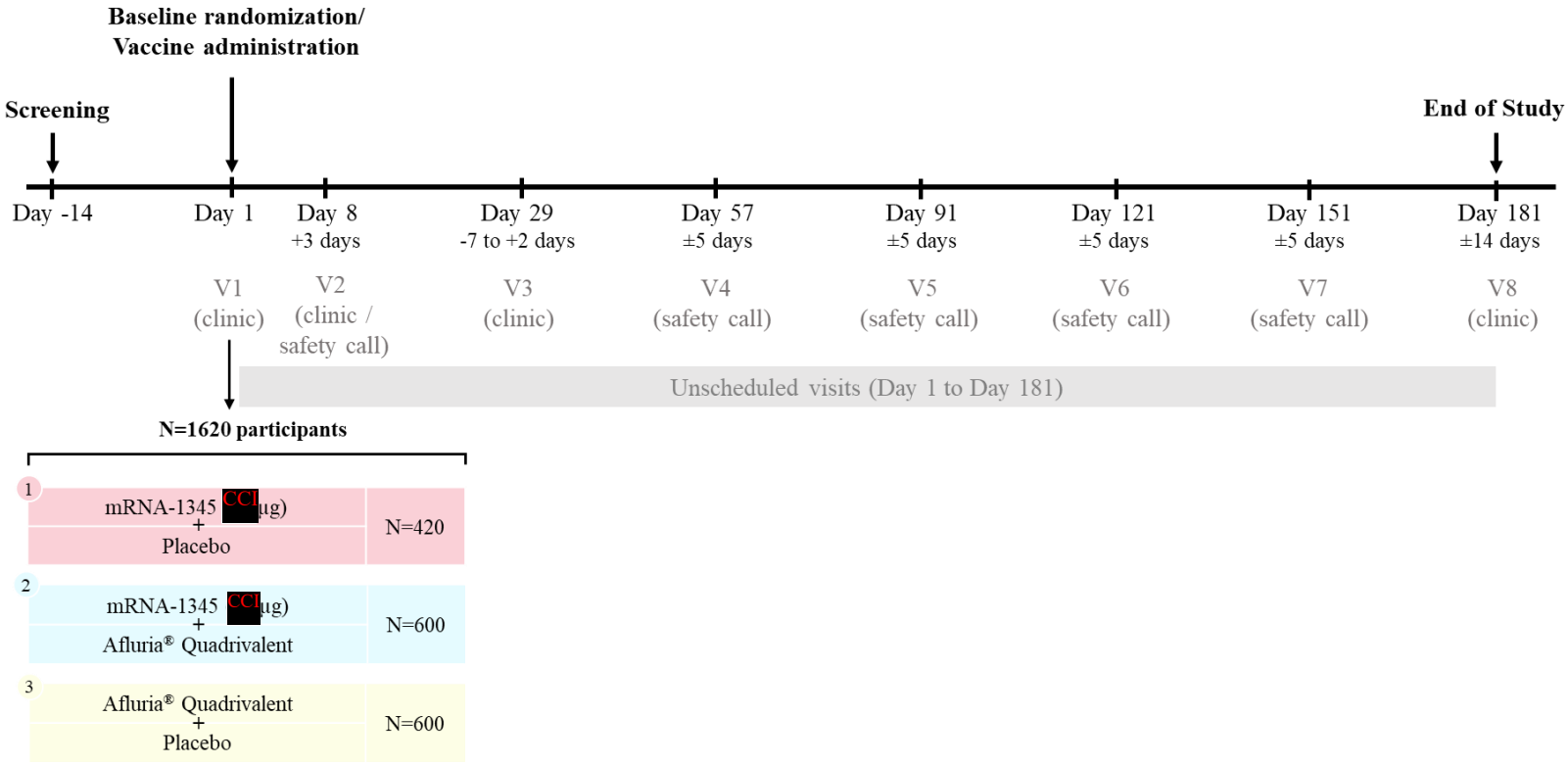
Note: Enrolled means participants', or their legally acceptable representatives', agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Data Monitoring/other Committee:

Safety monitoring for this study will include the blinded study team members, inclusive of, at a minimum, the Sponsor's medical monitor and a contract research organization (CRO) medical monitor, a blinded IST, and an unblinded DSMB. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the IST and DSMB of potential safety signal events. The IST will be composed of the Sponsor's physicians and may also include Sponsor-designated members from the CRO, as specified in the study IST charter. The IST will conduct ad hoc reviews as requested by the study medical monitor and study team. The DSMB, composed of external/independent subject matter experts, will conduct unblinded reviews of safety data on an ad hoc basis if requested by the study team and/or the IST.
This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

2.1.2. Schema (Part A)

Figure 1: Study Schema (Part A)



Abbreviation: V = visit.

2.1.3. SoA (Part A)

Table 1: SoA (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 Timepoint	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.

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.

2.2. Objectives and Endpoints (Part A)

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

Table 2: Study Objectives and Endpoints (Part A)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent)	• Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) over the 7 days post-injection • Numbers and percentages of unsolicited adverse events (AEs) through 28 days post-injection • Numbers and percentages of medically attended AEs (MAAEs), serious AEs (SAEs), adverse events of special interest (AESIs) and AEs leading to withdrawal Day 1 (baseline) to Day 181/ EoS
• To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A	• Geometric mean titer (GMT) of serum RSV-A neutralizing Abs at Day 29 • Seroresponse rate (SRR) in RSV-A neutralizing Abs at Day 29
• To evaluate the impact of coadministered RSV vaccine on the immune response to influenza	• GMT of serum Ab level as measured by hemagglutination inhibition (HAI) assay for influenza at Day 29
Key Secondary	
• To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-B	• GMT of serum RSV-B neutralizing Abs at Day 29 • SRR in RSV-B neutralizing Abs at Day 29
• To evaluate the impact of coadministered RSV vaccine on the immune response to influenza based on seroconversion from baseline	• Seroconversion rate (SCR) in influenza A and B strains at Day 29
Secondary	
• To evaluate Ab response to mRNA-1345 with and without a seasonal influenza vaccine (Afluria® Quadrivalent)	• GMT and geometric mean fold rise (GMFR) of post-injection/baseline titers to RSV-A neutralizing Abs up to Day 181/EoS • GMT and GMFR of post-injection/baseline titers to RSV-B neutralizing Abs up to Day 181/EoS

Objectives	Endpoints
	• Proportion of participants with ≥2-fold increases in RSV-A neutralizing Ab titers up to Day 181/EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-B neutralizing Ab titers up to Day 181/EoS
• To evaluate the Ab response to seasonal influenza vaccine (Afluria® Quadrivalent) with and without mRNA-1345	• SCR at Day 181/EoS in anti-HA Abs measured by HAI assay • GMT and GMFR of serum Ab level as measured by HAI assay for influenza up to Day 181/EoS
Exploratory (may be performed)	
• To further characterize the immune response across study vaccines	• Geometric mean concentration (GMC) and GMFR of post-injection/baseline titers to RSV-binding Abs up to Day 181/EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-binding Ab concentration up to Day 181/EoS • Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

2.3. Study Design

2.3.1. General Design (Part A)

This is a Phase 3, randomized, observer-blind study to evaluate the 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 study schema is presented in Figure 1.

The study will enroll approximately 1620 medically stable adults ≥50 years of age. The eligibility criteria are provided in Section 2.4. 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) + 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 3: 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

The Schedule of Assessments (SoA) is provided in Table 1.

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 electronic diary (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). Serious AEs, 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 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 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.

The IST will also conduct ad hoc reviews throughout the study as requested by the study medical monitor and study team. An independent, unblinded DSMB will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. The safety data will be reviewed according to intervals defined in the DSMB charter and will occur as needed when study stopping or pausing criteria are met or as otherwise requested by the study team and/or IST. See Section 2.7.6 for details on the IST and DSMB constituted in this study.

This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

2.3.2. Scientific Rationale for Study Design

This study is designed as a randomized, observer-blind study to evaluate the safety and immunogenicity of mRNA-1345 when coadministered with a commercial influenza vaccine (Afluria Quadrivalent) compared with either vaccine alone in medically stable older adults ≥50 years of age. Participants will receive either mRNA-1345 + placebo, mRNA-1345 + Afluria Quadrivalent, or Afluria Quadrivalent + placebo in contralateral arms.

Local solicited ARs will be recorded separately for each injection site from Day 1 through Day 7 using eDiaries. Unsolicited AEs will be recorded from Day 1 through Day 28. Recording of 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.

Humoral immune responses to both RSV and influenza will be examined at baseline and several time points throughout the study (Table 1).

2.3.3. Choice of Vaccine Dose

The CCI-µg dose of mRNA-1345 was selected for this study based on the mRNA-1345-P101 study data (Section 1.1.6).

2.3.4. EoS Definition

A participant is considered to have completed the study if he or she has completed the last scheduled procedure on Day 181 (ie, 6 months after administration of the investigational product (IP) on Day 1; Table 1).

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

2.4. Study Population (Part A)

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

2.4.1. Inclusion Criteria (Part A)

Participants are eligible to be included in the study only if all the following criteria apply:

1. Adults ≥50 years of age on the day of the Randomization Visit who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses, but should be medically stable as assessed by:
    - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity,
    - Absence of medical events qualifying as SAEs within 1 month of the planned vaccination on Day 1, and
    - Absence of known, current, and life-limiting diagnoses which, in the opinion of the investigator, would make completion of the protocol unlikely.
2. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as bilateral tubal ligation >1 year prior to Screening, bilateral oophorectomy, hysterectomy, or menopause. An FSH level may be measured at the discretion of the investigator to confirm menopausal status.
3. Female participants of childbearing potential may be enrolled in the study, if the participant: (1) has a negative urine pregnancy test at Screening and on the day of vaccination, (2) has practiced adequate contraception or has abstained from all activities that could lead to pregnancy for 28 days prior to vaccination, (3) has agreed to continue

adequate contraception through 3 months following the last injection, and (4) is not currently breastfeeding.

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

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Hormonal contraceptive in the form of a pill or patch
- Medroxyprogesterone injection (eg, Depo-Provera®)
- Etonogestrel implant (eg, Nexplanon®)
- Sterilization of a female participant's male partner prior to entry into the study
- Vasectomy for male participants

Note: Periodic abstinence (eg, calendar, ovulation, symptom-thermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

4. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
5. Able to comply with study requirements, including access to transportation for study visits.
6. Access to inbound and outbound telephone communication with caregivers and study staff.

2.4.2. Exclusion Criteria (Part A)

Participants are not eligible to be included in the study if any of the following criteria apply:

1. Participant is acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to or at Day 1. Participants meeting this criterion may be rescheduled within the 14day Screening window and will retain their initially assigned participant number.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication ≤60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
3. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease. Note: Human immunodeficiency virus (HIV) positive participants with CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load and an undetectable HIV RNA within the past 12 months (low level variations from 50 to 500 viral copies/mL which do not lead to changes in antiretroviral therapy is allowed) as determined from participant's medical records, are permitted.

4. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA vaccine(s) or commercially available influenza and any components of the mRNA or commercially available influenza vaccines.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. Diagnosis of malignancy within previous 10 years (excluding nonmelanoma skin cancer).
8. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
9. Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure >160 mmHg at the Screening or baseline (Day 1) visit.
10. Known history of hypotension or systolic blood pressure <85 mmHg at the Screening or baseline (Day 1) visit.
11. Diastolic blood pressure >90 mmHg at the Screening or baseline (Day 1) visit.
12. Known uncontrolled disorder of coagulation.
    Note: In the setting of well-controlled atrial fibrillation, prophylaxis for cardiovascular thromboembolism, or stroke with the following medications are allowed (aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin).
13. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
14. Participant has received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study injections (Day 1) or plans to receive a vaccine authorized or approved by a local health agency within 28 days after the study injections.
15. Prior participation in research involving receipt of any IP (drug/biologic/device including any investigational RSV product) within 45 days before the planned date of the Day 1 study injection.
16. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine ≤180 days prior to the Randomization Visit.
17. Participant has tested positive for influenza by local health authority approved testing methods ≤180 days prior to the Screening Visit.
18. Participant had significant exposure to someone with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or COVID-19 in the past 10 days, as defined by the US Centers for Disease Control and Prevention (CDC) as a close contact of someone who has had COVID19.

19. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
20. Receipt of systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study.
21. Participant has a history of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
22. Participant has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
23. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
24. Participant is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

2.4.3. Lifestyle Restrictions

Not applicable.

2.4.4. Screen Failures

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

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.

2.5. Study Treatment

2.5.1. Investigational Products Administered

mRNA-1345 is an LNP formulation consisting of mRNA sequences encoding the RSV fusion glycoprotein stabilized in the prefusion conformation.

Afluria Quadrivalent is an egg-based, inactivated influenza vaccine.

The placebo is 0.9% sodium chloride (normal saline) injection, US Pharmacopeia (USP) or European Pharmacopeia.

2.5.2. Randomization and Blinding

Randomization will be performed using an interactive response technology (IRT) system. Randomization is further described in Section 2.3.1.

2.5.2.1. Blinding

The study is observer-blind, such that only designated unblinded study personnel responsible for vaccine preparation, administration, and/or accountability will have access to study treatment assignments. Neither the participant, investigator, nor clinical staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study. The investigator may be unblinded in the event of an emergency (Section 2.5.2.2).

2.5.2.2. Unblinding

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 clinical study report (CSR).

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms. The Sponsor will remain blinded to the treatment assignment throughout the treatment period for each individual cohort/dose level of the study up until the specified timepoint in the interim analysis (IA), as outlined in Section 2.8.6.

2.5.3. Preparation, Handling, Storage, and Accountability

2.5.3.1. Preparation of Study Vaccine

mRNA-1345 will be provided as a sterile liquid for injection and will be a white to off white dispersion at a concentration of CCI [redacted]

Afluria Quadrivalent will be provided as a 0.5 mL, single-dose, pre-filled syringe.

mRNA-1345 and placebo preparation instructions are detailed in the Pharmacy Manual.

2.5.3.2. Study Vaccine Administration

mRNA-1345, Afluria Quadrivalent, and/or placebo will be administered as IM injections, one in each deltoid muscle on Day 1, according to the procedures specified in the Pharmacy Manual. Each arm (left and right) and the corresponding vaccine or placebo administered will be recorded by the unblinded site staff and will be kept confidential from other study documents/personnel before unblinding is authorized.

On Day 1, participants will be monitored for a minimum of 30 minutes after vaccination. Assessments will include vital sign measurements and monitoring for local or systemic ARs as shown in the SoA (Table 1).

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

2.5.3.3. Study Vaccine Delivery and Receipt

The Sponsor (or designee) is responsible for the following:

- Supplying mRNA-1345, Afluria Quadrivalent, and placebo (0.9% sodium chloride) to the study sites.
- Confirming the appropriate labeling of the IP, so it complies with the legal requirements of the US.

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

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

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

2.5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of the IP.

mRNA-1345 and Afluria Quadrivalent will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

2.5.3.5. Study Vaccine Storage

mRNA-1345 should be stored at –25 to –15 ºC (–13 to 5 ºF). mRNA-1345 must be received by a designated unblinded study personnel at the study site, handled and stored safely, kept in a secure location with restricted access (unblinded study personnel only), and protected from moisture and light until it is prepared for administration. Additional details are found in the Pharmacy Manual.

Afluria Quadrivalent should be stored at 2 to 8 ºC (36 to 47 ºF).

The 0.9% sodium chloride injection (USP or European Pharmacopeia) should be stored at 20 to 25 ºC (68 to 77 ºF) in a secure location with restricted access (unblinded study personnel only).

2.5.3.6. Study Vaccine Accountability

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

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

2.5.3.7. Study Vaccine Handling and Disposal

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

2.5.4. Study Intervention Compliance

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

The study site staff are responsible for ensuring that the participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete the visit within the defined visit window, as specified in the SoA (Table 1 [Part A] or Table 7 [Part B]). If a participant does not complete a visit within the defined time window, that visit will be classified as a missed visit, and the participant will continue with the subsequent scheduled visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

2.5.5. Prior and Concomitant Medications

2.5.5.1. Prior Medications and Therapies

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

2.5.5.2. Concomitant Medications and Therapies

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

- All nonstudy vaccinations administered within the period starting 28 days before the study injection and through Day 181/EoS.
- Seasonal influenza vaccine administered for the current influenza season (as appropriate for a study site depending on whether it is located in the Northern or Southern Hemisphere).
- All concomitant medications taken through 28 days after vaccination. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID19, RSV disease, or any other infectious disease symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or an MAAE from Day 1 through Day 181/EoS.
- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after vaccination, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study site visits or via other participant interactions (eg, safety telephone calls).
- Use of facial injections or dermal fillers, for cosmetic or medical indications such as migraine headaches.

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

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

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

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 2.8.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IPs used during the study period.
- A nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of the type of vaccine) administered during the period from 28 days before through 28 days after the study injection.
- Immunoglobulins and/or any blood products administered during the study period (except for treatment of COVID-19).

- Medications that suppress the immune system (except for treatment of COVID-19).

2.5.6. Intervention After the End of the Study

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

2.6. Delay or Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

2.6.1. Criteria for Delay of Vaccine Administration

2.6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature must be measured before vaccination. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may be injected at a later date within the time window specified in the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]), or the participant may be discontinued from dosing at the discretion of the investigator (Section 2.6.2):

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

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

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

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

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

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the medical monitor (Section 2.5.5.3).

2.6.2. Participant Discontinuation/Withdrawal from the Study

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

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

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

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

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

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

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

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

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 6.1.6).

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

2.6.3. Lost to Follow-Up

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

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

2.7. Study Assessments and Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF; Section 6.1.6). Participants will undergo study procedures at the time points specified in the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]). A participant can also attend an unscheduled visit at any time during the study. Reasons for an unscheduled visit may include, but are not limited to, reactogenicity issues or new or ongoing AEs. The study site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with the Food and Drug Administration guidance on the conduct of clinical trials of medical products during COVID-19 public health emergency (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the study.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The Screening Visit and Day 1 Visit may be performed on the same day. Additionally, the Screening Visit assessments may be performed over multiple visits if within the 14day Screening window.

2.7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]):

- Solicited local and systemic ARs (Section 2.7.4.3) that occur during the 7 days following vaccine administration (ie, the day of study injections and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 2.7.1.1). Local solicited ARs will be recorded separately for each injection site.
- Unsolicited AEs observed or reported from the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 2.7.4.1 and Section 2.7.4.2.
- SAEs, AESIs, MAAEs, and AEs leading to discontinuation from study participation from vaccination on Day 1 through EoS or withdrawal from the study.
- Vital sign measurements (Section 2.7.1.3).
- Physical examination findings (Section 2.7.1.4).

The incidence and severity of the above events will be monitored by an IST on a regular basis.

2.7.1.1. Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or a device that will be provided at the time of enrollment. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided with an eDiary device to record solicited ARs (Section 2.7.4.3).

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

On vaccination days, participants will record data in the eDiary starting approximately 30 min after administration of the IP under supervision of the study site staff to ensure correct completion of the eDiary. The study site staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the study site once per day, preferably in the evening and at the same time each day, on the day of vaccination and 6 subsequent days.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 2.7.4.3, that occur on the day of vaccination and during the 7 days after vaccination (ie, the day of injection and 6 subsequent days). Local solicited ARs will be recorded separately for each injection site. ARs beyond Day 7 should be reviewed either at the next scheduled study site visit or during the safety telephone call.
- Daily oral body temperature measurements should be performed using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.

- Other measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) should be performed using the ruler provided by the study site.
- Whether any medications were taken to treat or prevent pain or fever on the day of vaccination and 6 subsequent days.

The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

The study site staff will review eDiary data with participants during the Day 8 visit (Visit 2) (or Day 37 [Visit 4] for Part B) after vaccination.

2.7.1.1.1 Ancillary Supplies for Participant Use

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

2.7.1.2. Safety Telephone Call

The safety telephone call will be made to the participants by trained study site personnel. This call will follow a Sponsor-approved script, which will facilitate the collection of relevant safety information. Safety telephone calls by the study site to each participant will occur at the time points indicated in the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]). The participant will be interviewed according to the script about the occurrence of AEs, MAAEs, AESIs, SAEs, AEs leading to discontinuation, concomitant medications associated with those events, and any nonstudy vaccinations (Section 2.7.4.6). All safety information collected from the telephone call must be documented in the source documents as described by the participant and not documented on the script used for the safety telephone call. As noted in Section 2.7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

2.7.1.3. Vital Sign Measurements

Vital sign measurements include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the SoA (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]). On the day of IP administration, vital sign measurements will be collected once before and at least 30 minutes after vaccination. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented in the AE section of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional

assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, or is considered stable or until the investigator determines that follow-up is no longer medically necessary.

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

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

2.7.1.4. Physical Examinations

A full physical examination, including height and weight, will be performed at the Screening Visit (Table 1 [Part A], Table 7 [Part B], or Table 11 [Part C]). The full physical examination will include an assessment of the skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. At the Screening Visit, the participant's body mass index will be calculated using the formula weight (kg)/(height [m])^2. Any clinically significant findings identified should be reported as an MAAE.

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

2.7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoA (Table 1). Immunogenicity assessments will be performed for all participants. The following analytes will be measured:

- RSV Abs, as measured by nAbs and binding (bAbs).
- GMT of serum Ab level as measured by a HAI assay for influenza.

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

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

According to the ICF (Section 6.1.6), excess serum from the blood samples collected for immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to RSV and influenza virus and additional assay development.

2.7.3. Efficacy Assessments

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

2.7.4. Safety Definitions and Related Procedures

2.7.4.1. Adverse Event

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

Events Meeting the Adverse Event Definition:

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

Events NOT Meeting the Adverse Event Definition:

- Procedures planned before enrollment in the study (eg, hospitalization for preplanned surgical procedure).
- Medical or surgical procedures (eg, endoscopy or appendectomy). The condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 2.7.4.3). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the IP and AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol (Section 2.7.4.3) or specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, 7 days after vaccination).

2.7.4.2. Serious Adverse Events

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

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the IP.
- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as AEs; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE. Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure) are not considered SAEs.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.** This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect.**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

2.7.4.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after administration of the IP. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 2.7.1.1). Participants will record such occurrences in an eDiary from the day of injection and 6 subsequent days). Local solicited ARs will be recorded separately for each injection site.

Severity grading of reactogenicity will occur automatically based on participant entry in the eDiary according to the grading scales presented in Table 4 from the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS 2007).

If a participant reported a solicited adverse reaction during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity page of the eCRF. If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event on the

Reactogenicity page of the eCRF. If the participant reported an event that started after the solicited period, it should be recorded as an AE on the AE page of the eCRF. All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	25 – 50 mm/ 2.5 – 5 cm	51 – 100 mm/ 5.1 – 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	25 – 50 mm/ 2.5 – 5 cm	51 – 100 mm/ 5.1 – 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

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

Abbreviations: AE = adverse event; eCRF = electronic case report form.
Note: Events listed in the table above but starting >7 days after study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator.
Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

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

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP), to be recorded as an MAAE (Section 2.7.4.4).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days post-injection.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

2.7.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP, including telephone calls. This would include visits to a study site for unscheduled assessments (eg, rash assessment) and visits to HCPs external to the study site (eg, urgent care, primary care physician). The investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured on the AE page of the eCRF.

2.7.4.5. Adverse Event of Special Interest

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

Section 6.3 provides a list of the AESIs pertinent to this study.

All AESIs will be collected from Day 1 through EoS and must be reported to the Sponsor (or designee) immediately and in all circumstances within 24 hours of becoming aware of the event via the electronic data capture (EDC) system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox or the SAE Fax line (Section 2.7.4.10).

2.7.4.5.1 Anaphylaxis

All suspected cases of anaphylaxis should be recorded as MAAEs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor (or designee) immediately and in all circumstances within 24 hours per Section 2.7.4.10. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and based on the Brighton Collaboration case definition (Rüggeberg, et al 2007).

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

Anaphylaxis is a clinical syndrome characterized by the following:

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

2.7.4.5.2 Myocarditis/Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet the criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (Section 2.7.4.2). The CDC case definition is provided in Section 6.3.2 as guidance.

2.7.4.6. Eliciting and Documenting Adverse Events

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

Solicited ARs will be collected from the day of injection and 6 subsequent days. Other (unsolicited) AEs will be collected from the day of injection and 28 subsequent days.

The MAAEs, AESIs, AE leading to withdrawal, and SAEs will be collected from participants as specified in the SoA (Table 1 [Part A] Table 7 [Part B], or Table 11 [Part C]) until the end of their participation in the study. Any AEs occurring before administration of the IP will be analyzed separately from the AEs occurring after administration of the IP.

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent study site visits, safety telephone calls, and any other contact. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (Section 2.6.3). All contacts or contact attempts concerning the follow-up of AEs and SAEs should be recorded in the participant's source documentation.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 2.7.4.10).

2.7.4.7. Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined criteria as described in the definition of an SAE (Section 2.7.4.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 2.7.4.3.

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

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

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

2.7.4.8. Assessment of Causality

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

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

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

2.7.4.9. Reporting Adverse Events

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

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes the type of event, time of onset, investigator-specified assessment of the severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the

investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE. Medical conditions that begin after obtaining informed consent but before the IP administration will be recorded in the medical history/current medical conditions section in the eCRF and not in the AE section; however, if the medical condition worsens at any time during the study, it will be recorded and reported as an AE.

2.7.4.10. Reporting Serious Adverse Events

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

Any AE considered serious by the investigator or that meets SAE criteria (Section 2.7.4.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in 21 CFR Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Drugsafety@modernatx.com
- SAE Fax Line (USA and Canada): +1-617-649-3910

Regulatory reporting requirements for SAEs are described in Section 2.7.4.15.

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

2.7.4.11. Reporting of Adverse Events of Special Interest

The following process for reporting an AESI ensures compliance with 21 CFR 312 and ICH GCP guidelines. After learning that a participant has experienced an AESI, the investigator (or designee) is responsible for reporting the AESI to the Sponsor, regardless of its relationship to the IP or expectedness, within 24 hours of becoming aware of the event. If the AESI meets the criteria for an SAE, the SAE reporting procedure should be followed (Section 2.7.4.10).

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

Medical occurrences that begin before administration of the IP but after obtaining informed consent will be recorded in the “Medical History/Current Medical Conditions” section of the

eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected by:

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

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

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

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE or AESI form using the SAE Mailbox or the SAE Fax line (Section 2.7.4.10).

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

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

2.7.4.13. Method of Detecting AEs and SAEs

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

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

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

2.7.4.14. Follow-up of AEs and SAEs

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

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 2.6.3.

In the case of any SAE/AESI, the participant must be followed up until clinical recovery is complete or until the outcome has been stabilized. This may imply that follow-up could continue after the participant discontinues the trial, or after the intended duration of the safety follow-up for the study has been completed. In the case of any SAE or AESI brought to the attention of the investigator at any time after the end of the study for the participant and considered to be cause by mRNA-1345, the event must be reported to the SAE Mailbox, SAE Hotline, or SAE Fax Line, as noted in Section 2.7.4.10.

2.7.4.15. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

2.7.5. Pregnancy

Details of all pregnancies occurring in participants after the start of injection must be reported to the Sponsor or designee within 24 hours of learning of the pregnancy following the procedures outlined in Section 2.7.4.6. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Further information on the collection of pregnancy information is given in Section 2.7.4.6.

2.7.6. Safety Monitoring

Safety monitoring for this study will include the blinded study team members, inclusive of, at a minimum, the Sponsor's medical monitor and a CRO medical monitor, a blinded IST, and an unblinded DSMB. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the IST and DSMB of potential safety signal events. The

IST will be composed of the Sponsor's physicians and may also include Sponsor-designated members from the CRO, as specified in the study IST charter. The IST will conduct ad hoc reviews as requested by the study medical monitor and study team. The DSMB, composed of external/independent subject matter experts, will conduct unblinded reviews of safety data on an ad hoc basis if requested by the study team and/or the IST.

2.7.7. Treatment of Overdose

As the study treatment is to be administered by an HCP, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 6.1.8).

2.7.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

2.7.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

2.7.10. Biomarkers

Immunogenicity assessments are described in Section 2.7.2. Biomarker assessment may include genomic and transcriptomics samples.

2.7.11. Health Economics

Health economics are not evaluated in this study.

2.8. Statistical Considerations

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

2.8.1. Blinding and Responsibility for Analyses

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

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the IP for all participants. These personnel will have no study functions other than IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant or the blinded study

site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

- Unblinded medically qualified study site personnel will administer the IP. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned IA (Section 2.8.6). Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results to the blinded investigators, study site staff, clinical monitors, or participants.
- The DSMB will review the IA data to safeguard the interests of clinical study participants and to help ensure the integrity of the study. The DSMB will review unblinded IA results provided by the independent unblinded statistician. Section 2.7.6 provides additional information on DSMB and safety review.

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

2.8.1.1. Breaking the Blind

Except in the case of medical necessity, a participant's vaccine assignment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the vaccine assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual vaccine assignment, the investigator will make every attempt to contact the 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.

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

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified timepoint(s) for analysis as outlined in Section 2.8.1.

2.8.2. Statistical Hypotheses

The immunogenicity primary objectives are to evaluate the effect of coadministered influenza vaccine with mRNA-1345 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^1_0: 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 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that of participants who received mRNA-1345 plus placebo will be demonstrated by the lower bound (LB) of the 95% CI of the geometric mean titer ratio (GMR) of ruling out 0.667 (ie, LB > 0.667) using a 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^2_0: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by seroresponse rate (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 of participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out -10% (ie, LB > -10%) using a noninferiority margin of 10%. The SRR difference is the SRR of RSV-A nAb in participants who received mRNA-1345 coadministered with Afluria Quadrivalent minus the SRR of RSV-A nAbs in participants who received mRNA-1345 plus placebo.

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^3_0 to H^6_0: immunogenicity response to Afluria Quadrivalent in participants who received Afluria Quadrivalent coadministered with mRNA-1345, as measured by GMT of influenza anti-HA Abs for each of the 4 influenza strains at Day 29 using HAI assay, is inferior compared with 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 of 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 (ie, LB > 0.667) using a 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^7_0: 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 in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that of 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 (ie, 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 Afluria Quadrivalent compared with the GMT of RSV-A nAbs in participants who received mRNA-1345 plus placebo.

Key secondary endpoint based on SRR at Day 29:

The null hypothesis H^8_0: 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 the SRR in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that of participants who received mRNA-1345 plus placebo will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out -10% (ie, 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 minus the SRR of RSV-B nAb in participants who received mRNA-1345 plus placebo.

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^9_0 to H^{12}_0: immunogenicity response to Afluria Quadrivalent in participants who received mRNA-1345 coadministered with Afluria Quadrivalent, as measured by seroconversion rate (SCR) of influenza anti-HA Abs for each influenza strain at Day 29 using HAI assay, is inferior compared with that in participants who received Afluria Quadrivalent plus placebo. The noninferiority in SCR in participants who received mRNA-1345 coadministered with Afluria Quadrivalent compared with that of participants who received Afluria Quadrivalent plus placebo will be demonstrated by the LB of the 95% CI of the SCR difference of ruling out -10% (ie, LB > -10%) using a noninferiority margin of 10%. The SCR difference is the SCR of anti-HA Abs in participants who received mRNA-1345 coadministered with Afluria Quadrivalent minus the SCR of anti-HA Abs in participants who received Afluria Quadrivalent plus placebo.

2.8.3. Sample Size Determination

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

Assuming approximately 10% of participants are ineligible to be included in the PP Set; 540 participants receiving mRNA-1345 plus Afluria Quadrivalent (Group 2) and 378 participants receiving mRNA-1345 plus 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 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 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.

The global power considering meeting the primary objectives to evaluate the immune responses to RSV-A and influenza is at least 90%. Sample size justification for the co-primary endpoints is shown in Table 5.

Table 5: Sample Size Justification for the Co-primary Endpoints

Co-primary Endpoints	Number of Evaluable Participants (with 10% ineligible for the PP 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	378 (Group 1) 540 (Group 2)	0.05		SRR=0.8 in both groups	10%	96%

Co-primary Endpoints	Number of Evaluable Participants (with 10% ineligible for the PP Set)	α	Standard Deviation	GMR/SRR Assumed	NI Margin	Power
Coadministration (Group 2) vs. alone (Group 1)						
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%
Global power to show noninferiority of the co-primary immunogenicity endpoints						90%

Abbreviations: GMR = geometric mean titer ratio; GMT = geometric mean titer; PP = per protocol; SRR = seroresponse rate.

With 540 and 378 participants to be included in the PP Set in Group 2 and 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 at Day 29 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 the PP Set in Group 2 and Group 3, respectively, 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, the overall power to demonstrate the noninferiority of the immune response to 4 influenza strains is approximately 80%.

2.8.4. Analysis Sets

The analysis sets are described in Table 6 for Parts A and B and Table 13for Part C.

Table 6: Analysis Sets

Set	Description
Randomized Set	Includes all participants who are randomized in the study, regardless of the participant's treatment status in the study.

Set	Description
	Participants will be included in the vaccination group to which they are randomized.
Full Analysis Set (FAS)	All randomized participants who received any IP. Participants will be included in the vaccination group to which they are randomly assigned.
Per Protocol (PP) Set	Includes all participants in the FAS that received the assigned IP dose according to protocol, complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment, 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. Participants will be included in the vaccination group to which they are randomly assigned.
Solicited Safety Set	Includes all randomized participants who received any study vaccination and contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the IP they actually received.
Safety Set	Includes all randomized participants who receive any study injection. Participants will be included in the vaccination group corresponding to the IP they actually received for the analysis of safety data using the Safety Set.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; PP = per protocol.

2.8.5. Statistical Methods

2.8.5.1. Immunogenicity Analysis

The immunogenicity endpoints will be analyzed using the PP Set, by vaccination group. If the number of participants in the full analysis set (FAS) and PP Set differs (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

The co-primary and key secondary endpoints include the GMT of RSV-A/RSV-B nAb titers at Day 29 and GMT of anti-HA Ab titers for each influenza strain, as measured by HAI at Day 29. For each co-primary and key secondary endpoint regarding GMT, the GMR will be estimated using an analysis of covariance (ANCOVA) model on the log-transformed titers at Day 29, with the vaccination group as the fixed variable, log-transformed baseline titers as a fixed covariate, adjusted for stratified age group used for randomization. The geometric least square mean (GLSM) and its corresponding 95% CI in a log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale as an estimate of the GMT and its 95% CI. The GMR, estimated by the ratio of the GLSM and the corresponding 2-sided 95% CI, will be provided to assess the treatment difference. The corresponding 2-sided 95% CI of the GMR will be provided to assess the difference in the immune response between the

2 vaccination groups. For each co-primary and key secondary endpoint regarding GMT, the noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is > 0.667.

SRR of RSV-A/RSV-B nAbs is defined as proportion of participants with post-vaccination titers ≥4 × LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ. SCR of an influenza strain is defined as proportion of participants with a post-vaccination titer ≥1:40 if baseline is <1:10 or a ≥4-fold rise in post-vaccination HAI Ab titer if baseline is ≥1:10.

The number and percentage of participants with seroresponse or seroconversion at each postbaseline timepoint will be provided with 2-sided 95% CIs using the Clopper-Pearson method. For the co-primary endpoint and key secondary endpoints regarding SRR and SCR, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in the SRR or SCR at Day 29 between the vaccination groups. The noninferiority of the SRR at Day 29 for RSV-A/RSV-B nAbs will be demonstrated if the LB of the 95% CI of the SRR difference between mRNA-1345 + Afluria Quadrivalent coadministered and mRNA-1345 plus placebo groups is > –10%. The noninferiority of the SCR at Day 29 will be demonstrated if the LB of the 95% CI of the SCR difference between mRNA-1345 + Afluria Quadrivalent coadministered and Afluria Quadrivalent plus placebo groups is > –10%.

Data from quantitative immunogenicity assays will be summarized for each vaccination group using positive response rates and geometric means with 95% CIs for each timepoint an assessment is performed.

For the immunogenicity endpoints, the GMT/GMC ratio of specific Abs, with the corresponding 95% CI at each timepoint, and geometric mean fold rise of specific Ab titers, with the corresponding 95% CI at each postbaseline timepoint over preinjection baseline on Day 1, will be provided by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale descriptive summary statistics, including the median, minimum, and maximum values, will also be provided.

For summarizations of the GMT/GMC ratios, Ab titers reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ if actual values are not available.

The proportion of participants with at least 2-fold and at least 4-fold increases in titers/concentration (relative to baseline) will be provided by timepoint with the 2-sided 95% CI using the Clopper-Pearson method at Day 29. The number and percentage of participants with 2- and 4-fold increases will be provided with the 2-sided 95% CI using the Clopper-Pearson method. To compare the 2- and 4-fold increase rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in the fold-rise increase rates. The 2- and 4-fold rate difference, with the corresponding 95% CI at Day 29, will be provided.

Descriptive statistics (including 95% CIs) of the immunogenicity endpoints will also be provided by vaccination group and age group (50 to 59 years, 60 to 74 years, and ≥75 years).

2.8.5.2. Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, AEs leading to 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 system organ class and preferred term according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive 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 the vaccination group corresponding to the IP the participants actually received, unless otherwise specified. Local solicited reactogenicity analyses will be presented by injection content and vaccination group corresponding to the IP the participants actually received.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7-day follow-up period after administration of the IP will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to discontinuation from study participation in the study will be summarized.

The number of events of unsolicited AEs, SAEs, and MAAEs will be summarized.

For all other safety parameters, descriptive summary statistics will be provided.

The number and percentage of participants who have vital signs results below or above the normal ranges will be summarized by timepoint.

2.8.5.3. Exploratory Analyses

Exploratory analyses not addressed in Section 2.8.5.3 will be described in the SAP before database lock.

2.8.6. Planned Analyses

A primary analysis and a final analysis will be conducted in this study. Further details can be found in the SAP.

2.8.6.1. Primary Analysis

The primary analysis of safety and immunogenicity will be performed after all participants have completed the Day 29 Visit. All data relevant to the primary study analysis through the Day 29 visit will be cleaned and locked for the primary analysis (ie, data that are as clean as possible) and a report may be generated. The primary analysis will be performed by a separate team of unblinded programmers and statisticians.

2.8.6.2. Final Analysis

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

2.8.7. Multiplicity

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 endpoints.

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 successfully in order to declare the study a success to achieve noninferiority of coadministration.

The key secondary endpoints will be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all co-primary endpoints have achieved statistical significance.

3. PART B

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.

3.1. Protocol Summary

3.1.1. Synopsis (Part B)

Protocol Title:

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 1Year Following a Primary Dose in Adults ≥ 50 Years of Age

Regulatory Agency Identifier Numbers:

Investigational New Drug: 23342

Rationale:

This study is designed as a randomized, observer-blind study to evaluate the safety and immunogenicity of mRNA-1345 when coadministered with mRNA-1273.214 compared with either vaccine alone in medically stable older adults ≥50 years of age. Participants will receive either mRNA-1345 + placebo, mRNA-1345 + mRNA-1273.214, or mRNA-1273.214 + placebo in contralateral arms. If not received on Day 1, all remaining participants will receive mRNA-1273.214 on Day 29.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214	• Numbers and percentages of participants with solicited local and systemic ARs over the 7 days after each injection. • Numbers and percentages of unsolicited AEs through 28 days after each injection. • Numbers and percentages of MAAEs, SAEs, AESIs, and AEs leading to discontinuation from Day 1 (baseline) to EoS.
• To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-A	• GMT of serum RSV-A neutralizing Abs at Day 29. • SRR in RSV-A neutralizing Abs at Day 29.

Objectives	Endpoints
• To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2	• GMC of serum Ab level as measured by neutralization assay for SARS-CoV-2 at Day 29. • SRR for SARS-CoV-2 at Day 29.
Key Secondary	
• To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-B	• GMT of serum RSV-B neutralizing Abs at Day 29. • SRR in RSV-B neutralizing Abs at Day 29.
Secondary	
• To evaluate Ab response to mRNA-1345 with and without mRNA-1273.214	• GMT and GMFR of postinjection/baseline titers to RSV-A neutralizing Abs up to EoS. • GMT and GMFR of postinjection/baseline titers to RSV-B neutralizing Abs up to EoS. • Proportion of participants with ≥2-fold increases in RSV-A neutralizing Ab titers up to EoS. • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-B neutralizing Ab titers up to EoS.
• To evaluate the Ab response to mRNA-1273.214 with and without mRNA-1345	• GMC and GMFR as measured by neutralization assay for SARS-CoV-2 up to EoS. • SRR up to EoS as measured by neutralization assay for SARS-CoV-2.
Exploratory (may be performed)	
• To further characterize the immune response across study vaccines	• GMC and GMFR of postinjection/baseline titers to RSV-binding Abs up to EoS. • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-binding Ab concentration up to EoS. • GMC and GMFR of postinjection/baseline titers to SARS-CoV-2 binding Abs up to EoS. • Proportion of participants with ≥2-fold and ≥4-fold increases in SARS-CoV-2 binding Ab concentration up to EoS. • Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

Overall Design:

Part B is a Phase 3, randomized, observer-blind study to evaluate the 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 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 the below table 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 the table below, to allow all study participants to receive an mRNA-1273.214 booster vaccination.

Group Name	Sample Size	Vaccines 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

At the dosing visit 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 day of injection and the following 27 days. Serious AEs, MAAEs, AEs leading to withdrawal, and AESIs will be assessed from Day 1 through EoS.

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.

Brief Summary:

The purpose of this study is to assess the safety and immune response of mRNA-1345, an mRNA vaccine targeting RSV when given alone or coadministered with a SARS-CoV-2 vaccine in healthy older adults.

Study details include:

- The study duration will be up to 7 months.
- The treatment is 2 injections on Day 1 and 2 injections on Day 29.
- The visit frequency will be 3 visits in the first month (Days 1 [clinic], 8 [clinic or telephone call], and 29 [clinic]); a clinic or safety telephone call on Day 37; a clinic visit at Month 2, and 3 (one per month); safety telephone calls from Months 3 through 5, and clinic visits at Month 6 and 7.

Number of Participants:

Approximately 1680 participants will be enrolled.

Note: Enrolled means participants', or their legally acceptable representatives', agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Data Monitoring/other Committee:

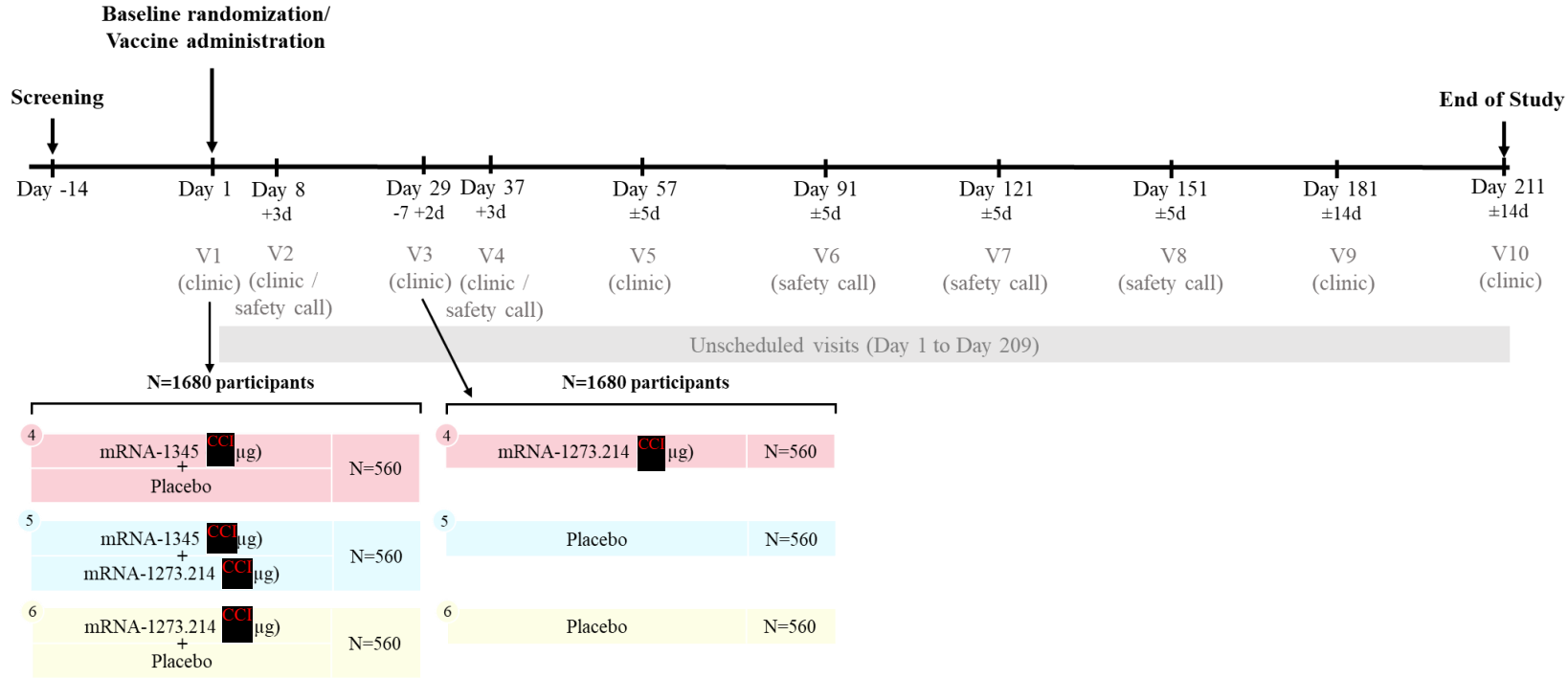
Safety monitoring for this study will include the blinded study team members, inclusive of, at a minimum, the Sponsor's medical monitor and a CRO medical monitor, a blinded IST, and an unblinded DSMB. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the IST and DSMB of potential safety signal events. The IST will be composed of the Sponsor's physicians and may also include Sponsor-designated members from the CRO, as specified in the study IST charter. The IST will conduct ad hoc reviews as requested by the study medical monitor and study team. The DSMB, composed of external/independent subject matter experts, will conduct unblinded reviews of safety data on an ad hoc basis if requested by the study team and/or the IST. This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

In addition, the following will be performed for Part B because of the inclusion of mRNA-1273.214 in the study design:

An independent Cardiac Event Adjudication Committee (CEAC) that includes cardiologists will review suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events and to assess severity. Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis, pericarditis, or myopericarditis will be referred to the Sponsor, who will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

3.1.2. Schema (Part B)

Figure 2: Study Schema (Part B)



3.1.3. SoA (Part B)

Table 7: SoA (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 Timepoint	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, 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 Timepoint	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 (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 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.

3.2. Objectives and Endpoints (Part B)

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

Table 8: Study Objectives and Endpoints (Part B)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of messenger RNA (mRNA)-1345 coadministered with mRNA-1273.214	• Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) over the 7 days after each injection • Numbers and percentages of unsolicited AEs through 28 days after each injection • Numbers and percentages of MAAEs, SAEs, AESIs, and AEs leading to discontinuation Day 1 (baseline) to EoS
• To evaluate the effect of coadministered mRNA-1273.214 on the immune response to respiratory syncytial virus (RSV)-A	• GMT of serum RSV-A neutralizing Abs at Day 29 • Seroresponse rate (SRR) in RSV-A neutralizing Abs at Day 29
• To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2	• GMC of serum Ab level as measured by neutralization assay for SARS-CoV-2 at Day 29 • SRR for SARS-CoV-2 at Day 29
Key Secondary	
• To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-B	• GMT of serum RSV-B neutralizing Abs at Day 29 • SRR in RSV-B neutralizing Abs at Day 29
Secondary	
• To evaluate Ab response to mRNA-1345 with and without mRNA-1273.214	• GMT and GMFR of postinjection/baseline titers to RSV-A neutralizing Abs up to EoS • GMT and GMFR of postinjection/baseline titers to RSV-B neutralizing Abs up to EoS • Proportion of participants with ≥2-fold increases in RSV-A neutralizing Ab titers up to EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-B neutralizing Ab titers up to EoS

Objectives	Endpoints
• To evaluate the Ab response to mRNA-1273.214 with and without mRNA-1345	• GMC and GMFR as measured by neutralization assay for SARS-CoV-2 up to EoS • SRR up to EoS as measured by neutralization assay for SARS-CoV-2
Exploratory (may be performed)	
• To further characterize the immune response across study vaccines	• GMC and GMFR of postinjection/baseline titers to RSV-binding Abs up to EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV-binding Ab concentration up to EoS • GMC and GMFR of postinjection/baseline titers to SARS-CoV-2 binding Abs up to EoS • Proportion of participants with ≥2-fold and ≥4-fold increases in SARS-CoV-2 binding Ab concentration up to EoS • Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

3.3. Study Design

3.3.1. General Design (Part B)

Part B is a Phase 3, randomized, observer-blind study to evaluate the 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 study schema is presented in Figure 2.

The study will enroll approximately 1680 medically stable adults ≥50 years of age. The eligibility criteria are provided in Section 3.4. 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 9 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 9 to allow all study participants to receive an mRNA-1273.214 booster vaccination.

Table 9: Randomized Groups (Part B)

Group Name	Sample Size	Vaccines 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

The SoA is provided in Table 7 and outlines all study visits.

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. Serious AEs, MAAEs, AEs leading to withdrawal, and AESIs will be assessed from Day 1 through EoS.

All study visit procedures and timing are described in the SoA (Table 7).

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.

Safety Oversight

An IST, inclusive of, at a minimum, the Sponsor's medical monitor, Sponsor's safety physician, and a CRO medical monitor, will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the data safety monitoring board (DSMB).

The IST will conduct a scheduled review of safety data after at least 30 participants (10 in each group in Part B) have completed the Day 8 visit. The IST will also conduct ad hoc reviews throughout the study as requested by the study medical monitor and study team.

An independent, unblinded DSMB will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. The safety data will be reviewed according to intervals defined in the DSMB charter and will occur as needed when study stopping or pausing criteria are met or as otherwise requested by the study team and/or IST. See Section 2.7.6 for details on the IST and DSMB constituted in this study.

This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

3.3.2. Scientific Rationale for Study Design

This study is designed as a randomized, observer-blind study to evaluate the safety and immunogenicity of mRNA-1345 when coadministered with mRNA-1273.214 compared with either vaccine alone in medically stable older adults ≥50 years of age. Participants will receive either mRNA-1345 + placebo, mRNA-1345 + mRNA-1273.214, or mRNA-1273.214 + placebo in contralateral arms. If not received on Day 1, all remaining participants will receive mRNA-1273.214 on Day 29 (Table 9).

3.3.3. Choice of Vaccine Dose

The [redacted]-µg dose of mRNA-1345 was selected for this study based on the mRNA-1345-P101 study data (Section 1.1.6).

The [redacted]-µg booster dose of mRNA-1273.214 was selected for this study based on the dose chosen for other Phase 3 mRNA-1273/1273.214 clinical studies.

3.3.4. EoS Definition

A participant is considered to have completed the study if he or she has completed the last scheduled procedure on Day 211 (ie, 6 months after administration of the last IP injection on Day 29; Table 7).

The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure, as shown in the SoA (Table 7).

3.4. Study Population

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

3.4.1. Inclusion Criteria (Part B)

Participants are eligible to be included in the study only if all the following criteria apply:

1. Adults ≥50 years of age on the day of the Randomization Visit who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses but should be medically stable as assessed by:
    - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity,
    - Absence of medical events qualifying as SAEs within 1 month of the planned vaccination on Day 1, and
    - Absence of known, current, and life-limiting diagnoses, which, in the opinion of the investigator, would make completion of the protocol unlikely.
2. Fully vaccinated for COVID-19 with an approved primary series according to the locally authorized or approved regimen. If the most recent COVID-19 vaccine was part of a primary series, it must be ≥150 days before (or less per local guidance) Day 1. If the most

recent COVID-19 vaccine was a booster dose, it must be ≥120 days before (or less per local guidance) Day 1.

3. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as bilateral tubal ligation >1 year prior to Screening, bilateral oophorectomy, hysterectomy, or menopause. An FSH level may be measured at the discretion of the investigator to confirm menopausal status.
4. Female participants of childbearing potential may be enrolled in the study if the participant: (1) has a negative urine pregnancy test at Screening and on the day of vaccination, (2) has practiced adequate contraception or has abstained from all activities that could lead to pregnancy for 28 days prior to vaccination, (3) has agreed to continue adequate contraception through 3 months following the last injection, and (4) is not currently breastfeeding.

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

   – Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
   – Intrauterine device
   – Hormonal contraceptive in the form of a pill or patch
   – Medroxyprogesterone injection (eg, Depo-Provera®)
   – Etonogestrel implant (eg, Nexplanon®)
   – Sterilization of a female participant's male partner prior to entry into the study
   – Vasectomy for male participants

   Note: Periodic abstinence (eg, calendar, ovulation, symptom-thermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
5. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
6. Able to comply with study requirements, including access to transportation for study visits.
7. Access to inbound and outbound telephone communication with caregivers and study staff.

3.4.2. Exclusion Criteria (Part B)

Participants are not eligible to be included in the study if any of the following criteria apply:

1. Participant is acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to or at Day 1. Participants meeting this criterion may be rescheduled within the 14-day Screening window and will retain their initially assigned participant number.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of

immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication ≤30 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

3. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease. Note: Participants who are HIV positive with CD4 count ≥350 cells/mm^3, an undetectable HIV viral load, and an undetectable HIV RNA within the past 12 months (low level variations from 50 to 500 viral copies/mL which do not lead to changes in antiretroviral therapy is allowed) as determined from participant's medical records, are permitted.
4. Conditions that could affect local solicited AR assessments as determined by the investigator (eg, tattoos, psoriasis patches affecting skin over either deltoid area).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA vaccine(s) or any components of the mRNA vaccines.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. Diagnosis of malignancy within previous 10 years (excluding nonmelanoma skin cancer).
8. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
9. Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure >160 mm Hg at the Screening or baseline (Day 1) visit.
10. Known history of hypotension or systolic blood pressure <85 mm Hg at the Screening or baseline (Day 1) visit.
11. Diastolic blood pressure >90 mm Hg at the Screening or baseline (Day 1) visit.
12. Known uncontrolled disorder of coagulation.
    Note: In the setting of well-controlled atrial fibrillation, prophylaxis for cardiovascular thromboembolism, or stroke with the following medications are allowed: aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin.
13. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
14. Participant has received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study injections (Day 1) or plans to receive a vaccine authorized or approved by a local health agency within 28 days after the study injections (with the exception of SARS-Cov-2 vaccination as defined in Inclusion Criterion 2).

15. Prior participation in research involving receipt of any IP (drug/biologic/device with the exception of RSV investigation products [see exclusion criterion 16]) within 45 days before the planned date of the Day 1 study injection.
16. Prior receipt of any investigational/approved RSV product within 1 year of the Day 1 study injection.
17. Participant had significant exposure to someone with SARS-CoV-2 infection or COVID-19 in the past 10 days, as defined by the US CDC as a close contact of someone who has had COVID19.
18. Has known history of SARS-CoV-2 infection within 90 days prior to enrollment.
19. Receipt of systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study.
20. Participant has a history of myocarditis, pericarditis, or myopericarditis.
21. Participant has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
22. Participant is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.
23. Participant has a history of dermatological filler injections.

3.4.3. Lifestyle Restrictions

Not applicable.

3.4.4. Screen Failures

See Section 2.4.4 for details.

3.5. Study Treatment

3.5.1. Investigational Products Administered

mRNA-1345 is an LNP formulation consisting of mRNA sequences encoding the RSV fusion glycoprotein stabilized in the prefusion conformation.

mRNA-1273.214 is based on the same platform as mRNA-1345. mRNA-1273.214 contains CX-024414, the mRNA that encodes for the S-2P of the Wuhan-Hu-1 isolate of SARS-CoV-2 and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant.

The placebo is 0.9% sodium chloride (normal saline) injection, USP or European Pharmacopeia.

3.5.2. Randomization and Blinding

Randomization will be performed using an IRT system. Randomization is further described in Section 3.3.1.

3.5.2.1. Blinding

See Section 2.5.2.1 for details.

3.5.2.2. Unblinding

See Section 2.5.2.2 for details.

3.5.3. Preparation, Handling, Storage, and Accountability

3.5.3.1. Preparation of Study Vaccine

mRNA-1345 will be provided as a sterile liquid for injection and will be a white to off white dispersion at a concentration of CCI [redacted]

mRNA-1273.214 will be provided as a sterile liquid for injection and will be a white to off white dispersion at a concentration of CCI [redacted]

mRNA-1345, mRNA-1273.214, and placebo preparation instructions are detailed in the Pharmacy Manual.

3.5.3.2. Study Vaccine Administration

mRNA-1345, mRNA-1273.214, and/or placebo will be administered as IM injections, one in each deltoid muscle at the times indicated in the SoA (Table 7), according to the procedures specified in the Pharmacy Manual. Each arm (left and right) and the corresponding vaccine or placebo administered will be recorded by the unblinded site staff and will be kept confidential from other study documents/personnel before unblinding is authorized.

Participants will be monitored for a minimum of 30 minutes after any injection. Assessments will include vital sign measurements and monitoring for local or systemic ARs as shown in the SoA (Table 7).

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

3.5.3.3. Study Vaccine Delivery and Receipt

The Sponsor (or designee) is responsible for the following:

- Supplying mRNA-1345, mRNA-1273.214, and placebo (0.9% sodium chloride) to the study sites.
- Confirming the appropriate labeling of the IP, so it complies with the legal requirements of the US.

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

- Confirming that the IP was received in good condition.
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate.

- Confirming that the Sponsor has authorized the IP for use.
- Ensuring the appropriate dose of the IP is properly prepared using aseptic technique.

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

3.5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of the IP.

mRNA-1345 and mRNA-1273.214, will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, the ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

3.5.3.5. Study Vaccine Storage

mRNA-1345 should be stored at –25 ºC to –15 ºC (–13 ºF to 5 ºF). mRNA-1273.214 must be stored at -90 °C to -60°C (-130 °F to -76 °F). mRNA-1345 and mRNA-1273.214 must be received by a designated unblinded study personnel at the study site, handled and stored safely, kept in a secure location with restricted access (unblinded study personnel only), and protected from moisture and light until it is prepared for administration. Additional details are found in the Pharmacy Manual.

The 0.9% sodium chloride injection (USP or European Pharmacopeia) should be stored at 15ºC to 25ºC (68ºF to 77ºF) in a secure location with restricted access (unblinded study personnel only).

3.5.3.6. Study Vaccine Accountability

See Section 2.5.3.6 for details.

3.5.3.7. Study Vaccine Handling and Disposal

See Section 2.5.3.7 for details.

3.5.4. Study Intervention Compliance

See Section 2.5.4 for details.

3.5.5. Prior and Concomitant Medications

3.5.5.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF. A complete history (at any time prior to informed consent) about prior COVID-19 vaccination will also be collected.

3.5.5.2. Concomitant Medications and Therapies

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

- All nonstudy vaccinations administered within the period starting 28 days before the study injection and through EoS.
- All concomitant medications taken through 28 days after vaccination. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19, RSV disease, or any other infectious disease symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or an MAAE from Day 1 through EoS.
- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after vaccination, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study site visits or via other participant interactions (eg, safety telephone calls).
- Use of facial injections or dermal fillers, for cosmetic or medical indications such as migraine headaches.

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

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

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

See Section 2.5.5.3 for details.

3.5.6. Intervention After the End of the Study

See Section 2.5.6 for details.

3.6. Delay or Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

3.6.1. Criteria for Delay of Vaccine Administration

3.6.1.1. Individual Participant Criteria for Delay of Study Vaccination

See Section 2.6.1.1 for details.

3.6.2. Participant Discontinuation/Withdrawal From the Study

See Section 2.6.2 for details.

3.6.3. Lost to Follow-Up

See Section 2.6.3 for details.

3.7. Study Assessments and Procedures

See Section 2.7 for details and refer to the SoA for Part B (Table 7).

3.7.1. Safety Assessments and Procedures

See Section 2.7.1 for details and refer to the SoA for Part B (Table 7).

In addition, for Part B, the following will be performed:

Any reverse transcriptase-polymerase chain reaction–confirmed case of RSV or any positive SARS-CoV-2 testing by an authorized/approved lateral flow/rapid antigen or polymerase chain reaction will be recorded as unsolicited AEs through EoS (unless they meet the definition of an SAE, MAAE, or AE leading to discontinuation).

3.7.1.1. Use of Electronic Diaries

See Section 2.7.1.1 for details and refer to the SoA for Part B (Table 7).

3.7.1.1.1 Ancillary Supplies for Participant Use

See Section 2.7.1.1.1 for details.

3.7.1.2. Safety Telephone Call

See Section 2.7.1.2 for details and refer to the SoA for Part B (Table 7).

3.7.1.3. Vital Sign Measurements

See Section 2.7.1.3 for details and refer to the SoA for Part B (Table 7).

3.7.1.4. Physical Examinations

See Section 2.7.1.4 for details and refer to the SoA for Part B (Table 7).

3.7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoA (Table 7). Immunogenicity assessments will be performed for all participants. The following analytes will be measured:

- RSV Abs, as measured by neutralization assay (nAbs) and binding assay (bAbs).
- SARS-Cov2 Abs, as measured by neutralization assay (nAbs) and binding assay (bAbs).

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

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

According to the ICF (Section 6.1.6), excess serum from the blood samples collected for immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to respiratory viruses (eg, RSV and SARS-CoV-2) and additional assay development.

3.7.3. Efficacy Assessments

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

3.7.4. Safety Definitions and Related Procedures

3.7.4.1. Adverse Event

See Section 2.7.4.1 for details and refer to the SoA for Part B (Table 7).

3.7.4.2. Serious Adverse Events

See Section 2.7.4.2 for details and refer to the SoA for Part B (Table 7).

3.7.4.3. Solicited Adverse Reactions

See Section 2.7.4.3 for details and refer to the SoA for Part B (Table 7).

3.7.4.4. Medically Attended Adverse Events

See Section 2.7.4.4 for details.

3.7.4.5. Adverse Event of Special Interest

See Section 2.7.4.5 for details.

3.7.4.6. Eliciting and Documenting Adverse Events

See Section 2.7.4.6 for details and refer to the SoA for Part B (Table 7).

3.7.4.7. Assessment of Intensity

See Section 2.7.4.7 for details and refer to the SoA for Part B (Table 7).

3.7.4.8. Assessment of Causality

See Section 2.7.4.8 for details and refer to the SoA for Part B (Table 7).

3.7.4.9. Reporting Adverse Events

See Section 2.7.4.9 for details and refer to the SoA for Part B (Table 7).

3.7.4.10. Reporting Serious Adverse Events

See Section 2.7.4.10 for details and refer to the SoA for Part B (Table 7).

3.7.4.11. Reporting of Adverse Events of Special Interest

See Section 2.7.4.11 for details and refer to the SoA for Part B (Table 7).

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

See Section 2.7.4.12 for details and refer to the SoA for Part B (Table 7).

3.7.4.13. Method of Detecting AEs and SAEs

See Section 2.7.4.13 for details and refer to the SoA for Part B (Table 7).

3.7.4.14. Follow-up of AEs and SAEs

See Section 2.7.4.14 for details and refer to the SoA for Part B (Table 7).

3.7.4.15. Regulatory Reporting Requirements for SAEs

See Section 2.7.4.15 for details and refer to the SoA for Part B (Table 7).

3.7.5. Pregnancy

See Section 2.7.5 for details and refer to the SoA for Part B (Table 7).

3.7.6. Safety Monitoring

See Section 2.7.6 for details and refer to the SoA for Part B (Table 7). In addition, the following will be performed for Part B because of the inclusion of mRNA-1273.214 in the study design:

An independent CEAC that includes cardiologists will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis, pericarditis, or myopericarditis will be referred to the Sponsor, who will then make a final decision on whether

to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

3.7.7. Treatment of Overdose

See Section 2.7.7 for details.

3.7.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

3.7.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

3.7.10. Biomarkers

Immunogenicity assessments are described in Section 3.7.2. Biomarker assessment may include genomic and transcriptomics samples.

3.7.11. Health Economics

Health economics are not evaluated in this study.

3.8. Statistical Considerations

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

3.8.1. Statistical Methods

3.8.1.1. Immunogenicity Analysis

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

The co-primary and key secondary endpoints include the GMT of RSV-A/RSV-B nAb titers at Day 29 and GMC of nAbs for each of the 2 SARS-CoV-2 strains, as measured at Day 29. For each co-primary and key secondary endpoint regarding GMT, the GMR will be estimated using an ANCOVA model on the log-transformed titers at Day 29, with the vaccination group as the

fixed variable, log-transformed baseline titers as a fixed covariate, adjusted for stratified age group used for randomization. The GLSM and its corresponding 95% CI in a log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale as an estimate of the GMT and its 95% CI. The GMR, estimated by the ratio of the GLSM and the corresponding 2-sided 95% CI, will be provided to assess the treatment difference. The corresponding 2-sided 95% CI of the GMR will be provided to assess the difference in the immune response between the 2 vaccination groups. For each co-primary and key secondary endpoint regarding GMT, the noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is > 0.667.

SRR of RSV-A nAbs, RSV-B nAbs, or a SARS-CoV-2 strain nAbs is defined as proportion of participants with post-vaccination titers ≥4 × LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ. The number and percentage of participants with seroresponse at each postbaseline timepoint will be provided with 2-sided 95% CIs using the Clopper-Pearson method. For the co-primary endpoint and key secondary endpoints regarding SRR, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in the SRR at Day 29 between the vaccination groups. The noninferiority of the SRR at Day 29 for RSV-A nAbs or RSV-B nAbs, will be demonstrated if the LB of the 95% CI of the SRR difference between mRNA-1345 plus mRNA-1273.214 followed with a subsequent injection of placebo and mRNA-1345 plus placebo followed with a subsequent injection of mRNA-1273.214 groups is > –10%. The noninferiority of the SRR at Day 29 for nAbs of SARS-CoV-2 Wuhan-Hu-1 or B1.1.529 strain will be demonstrated if the LB of the 95% CI of the SRR difference between mRNA-1345 plus mRNA-1273.214 followed with a subsequent injection of placebo and mRNA-1273.214 plus placebo followed with a subsequent injection of placebo groups is > –10%.

Data from quantitative immunogenicity assays will be summarized for each vaccination group using positive response rates and geometric means with 95% CIs for each timepoint an assessment is performed.

For the immunogenicity endpoints, the GMT ratio or GMC ratio of specific Abs, with the corresponding 95% CI at each timepoint, and GMFR of specific Ab titers, with the corresponding 95% CI at each postbaseline timepoint over preinjection baseline, will be provided by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale descriptive summary statistics, including the median, minimum, and maximum values, will also be provided.

For summarizations of the GMT ratios or GMC ratios, Ab titers reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values greater than the ULOQ will be converted to the ULOQ if actual values are not available.

The proportion of participants with at least 2-fold and at least 4-fold increases in titers/concentration (relative to baseline) will be provided by timepoint with the 2-sided 95% CI using the Clopper-Pearson method at Day 29. The number and percentage of participants with 2- and 4-fold increases will be provided with the 2-sided 95% CI using the Clopper-Pearson method. To compare the 2- and 4-fold increase rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in the fold-rise increase rates. The 2- and 4-fold rate difference, with the corresponding 95% CI at Day 29, will be provided.

Descriptive statistics (including 95% CIs) of the immunogenicity endpoints will also be provided by vaccination group and age group (50 to 59 years, 60 to 74 years, and ≥75 years).

3.8.1.2. Safety Analyses

See Section 2.8.5.2 for details. In addition, for Part B, the following will be performed:

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7 day follow-up period after administration of the IP at Day 29 will also be summarized respectively.

3.8.1.3. Exploratory Analyses

See Section 2.8.5.3 for details.

3.8.2. Blinding and Responsibility for Analyses

See Section 2.8.1 for details.

3.8.2.1. Breaking the Blind

See Section 2.8.1.1 for details.

3.8.3. Statistical Hypotheses

The immunogenicity primary objectives are to evaluate the effect of coadministered mRNA-1273.214 with mRNA-1345 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^1_0: 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 (ie, LB > 0.667) using a 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^2_0: 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 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% (ie, LB > -10%) using a noninferiority margin of 10%. The SRR difference is the SRR of RSV-A nAb in participants who received mRNA-1345 coadministered with mRNA-1273.214 at Day 1 minus the SRR of RSV-A nAbs in participants who received mRNA-1345 plus placebo at Day 1.

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^3_0 and H^4_0: 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 neutralizing Abs (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. For each of the two 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 (ie, LB > 0.667) using a 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.

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

The null hypothesis H^5_0 and H^6_0: 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) on 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% (ie, 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^7_0: 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 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 (ie, 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-A nAbs in participants who received mRNA-1345 plus placebo at Day 1.

Key secondary endpoint based on SRR at Day 29:

The null hypothesis H^8_0: 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% (ie, 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.

3.8.4. Sample Size Determination

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 mRNA-1345 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.

Assuming approximately 10% of participants are ineligible to be included in the PP Set, there are 504 eligible participants in each group:

- 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%.
- The global power considering meeting the primary objectives to evaluate the immune responses to RSV-A and SARS-CoV-2 is at least 90%. Sample size justification for the co-primary endpoints is shown in Table 10.

Table 10: Sample Size Justification for the Co-primary Endpoints

Co-primary Endpoints	Number of Evaluable Participants (with 10% ineligible for the PP 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 NI of the co-primary immunogenicity endpoints						90%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; GMC = geometric mean concentration; NI = noninferiority PP = per protocol; SRR = seroresponse rate.

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%.

3.8.5. Analysis Sets

See Section 2.8.4 for details.

3.8.6. Planned Analyses

A primary analysis and a final analysis will be conducted in this study. Further details can be found in the SAP.

3.8.6.1. Primary Analysis

See Section 2.8.6.1 for details.

3.8.6.2. Final Analysis

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 209/EoS.

3.8.7. Multiplicity

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 endpoints.

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 in Part B need to be met successfully to declare the study a success in Part B to achieve noninferiority of coadministration.

The key secondary endpoints will be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all co-primary endpoints have achieved statistical significance.

4. PART C

Part C is a Phase 3 single arm, open-label study to evaluate safety, tolerability, and immunogenicity of a booster dose (BD) of mRNA-1345 given at 1 year following a primary dose in adults ≥50 years of age.

4.1. Protocol Summary

4.1.1. Synopsis (Part C)

Protocol Title:

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.

Regulatory Agency Identifier Numbers:

Investigational New Drug: 23342

Rationale:

This study is designed as a single arm, open-label study to evaluate safety, tolerability, and immunogenicity of a BD of mRNA-1345 in adults ≥50 years of age who have previously received a primary dose of mRNA-1345. The mRNA-1345 recipients in the PP set in Part B (Group 4 [mRNA-1345 + placebo] and Group 5 [mRNA-1345 + mRNA-1273.214]) of this study who are willing to enroll in Part C will be screened accordingly. In Part C, eligible participants will receive mRNA-1345 boost at 1 Year following the primary dose.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• Numbers and percentages of participants with solicited local and systemic ARs through 7 days postBD. • Numbers and percentages of unsolicited AEs through 28 days postBD. • Numbers and percentages of MAAEs from BD Day 1 through BD Day 181. • Numbers and percentages of SAEs, AESIs, and AEs leading to discontinuation from BD Day 1 through BD Day 361/EoS.
• To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• GMT ratio of serum RSV-A neutralizing Abs at BD Day 29 over serum RSV-A-neutralizing Abs at Day 29 post primary dose.

Objectives	Endpoints
• To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• GMT ratio of serum RSV-B neutralizing Abs at BD Day 29 over serum RSV-B-neutralizing Abs at Day 29 post primary dose.
Secondary	
• 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	• Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A neutralizing Abs at BD Day 29. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B neutralizing Abs at BD Day 29.
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 at all evaluable immunogenicity assessment timepoints.	• GMT and GMFR of postBD/baseline titers to RSV-A neutralizing Abs up to BD Day 361/EoS. • GMT and GMFR of postBD/baseline titers to RSV-B neutralizing Abs up to BD Day 361/EoS. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A neutralizing Abs up to BD Day 361/EoS. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B neutralizing Abs up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline in RSV-A neutralizing Ab titers up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline in RSV-B neutralizing Ab titers up to BD Day 361/EoS.
Exploratory (may be performed)	
• To further characterize the immune response of a BD of mRNA-1345.	• GMC and GMFR of postBD/baseline titers to RSV-binding Abs up to BD Day 361/EoS. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-binding Ab concentration up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-binding Ab concentration up to BD Day 361/EoS.

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

Abbreviations: Ab = antibody, AE = adverse event, AR = adverse reaction, AESI = adverse event of special interest, BD = booster dose, EoS = end of study, GMC = geometric mean concentration, GMFR = geometric mean fold rise, GMT = geometric mean titer, MAAE = medically attended adverse event, RSV = respiratory syncytial virus, SAE = serious adverse event.

Overall 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 (Table 11). The study schema is presented in Figure 3.

The study will enroll approximately 500 adults ≥50 years of age who are medically stable. The eligibility criteria are provided in Section 4.4. On BD Day 1, each participant will receive one IM injection of mRNA-1345 ([redacted] µg) administered into the deltoid muscle of either the right or left arm.

Participants will have scheduled visits and safety calls according to the timepoints specified in the SoA (Table 11). 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 (ie, 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.

Brief Summary:

The purpose of this study is to assess the safety, tolerability, and immunogenicity of a BD of mRNA-1345 given at 1 year following a primary dose in adults ≥50 years of age.

Study details include:

- The study duration will be up to 1 year from the injection at BD Day 1.
- The vaccination of mRNA-1345 ([redacted] µg) will include 1 injection on BD Day 1.
- Details about the safety telephone call and visit frequency can be found in the SoA.

Number of Participants:

Approximately 500 participants will be enrolled.

Note: Enrolled means participant agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

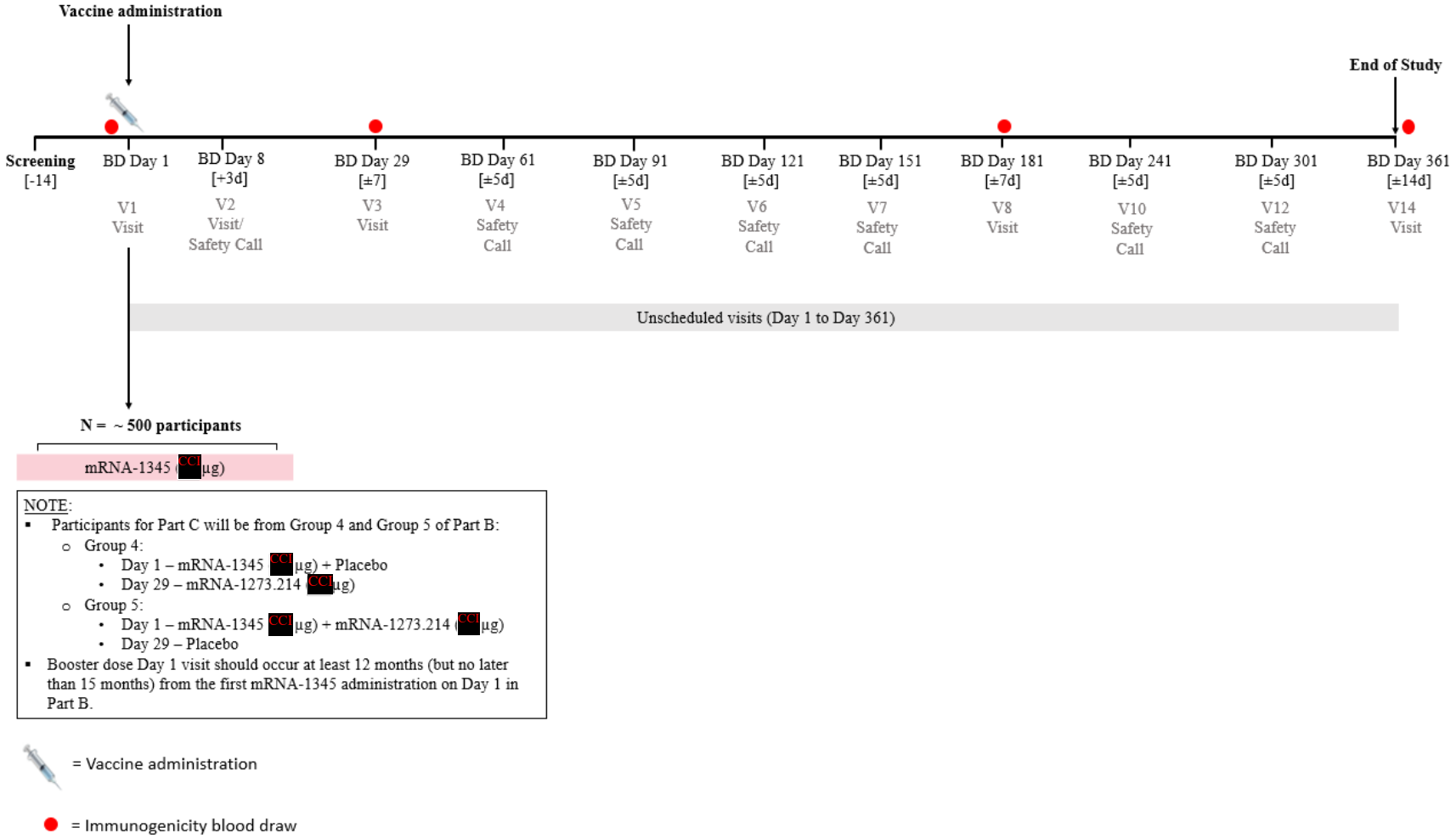
Prospective approval of protocol deviations for recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Data Monitoring/Other Committee:

Safety monitoring for this study will include the study team members inclusive of, at a minimum, the Sponsor's Medical Monitor and Safety Physician and a CRO Medical Monitor. The study team will conduct ongoing safety reviews during the study. This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

4.1.2. Schema (Part C)

Figure 3: Study Schema (Part C)



Abbreviations: BD = booster dose, d = days, V = visit.

4.1.3. SoA (Part C)

Table 11: SoA (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	–

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
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	–	–	–	–	–	–
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.

4.2. Objectives and Endpoints (Part C)

The objectives and endpoints of this study are described in Table 12.

Table 12: Study Objectives and Endpoints (Part C)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• Numbers and percentages of participants with solicited local and systemic ARs through 7 days postBD. • Numbers and percentages of unsolicited AEs through 28 days postBD. • Numbers and percentages of MAAEs from BD Day 1 through BD Day 181. • Numbers and percentages of SAEs, AESIs, and AEs leading to discontinuation from BD Day 1 through BD Day 361/EoS.
• To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• GMT ratio of serum RSV-A neutralizing Abs at BD Day 29 over GMT of serum RSV-A-neutralizing Abs at Day 29 post primary dose.
• To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• GMT ratio of serum RSV-B neutralizing Abs at BD Day 29 over GMT of serum RSV-B-neutralizing Abs at Day 29 post primary dose.
Secondary	
• 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	• Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A neutralizing Abs at BD Day 29. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B neutralizing Abs at BD Day 29.
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 at all evaluable immunogenicity assessment timepoints.	• GMT and GMFR of postBD/baseline titers to RSV-A neutralizing Abs up to BD Day 361/EoS. • GMT and GMFR of postBD/baseline titers to RSV-B neutralizing Abs up to BD Day 361/EoS. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-A neutralizing Abs up to BD Day 361/EoS.

Objectives	Endpoints
	• Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-B neutralizing Abs up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-A neutralizing Ab titers up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-B neutralizing Ab titers up to BD Day 361/EoS.
Exploratory (may be performed)	
• To further characterize the immune response of a BD of mRNA-1345.	• GMC and GMFR of postBD/baseline titers to RSV-binding Abs up to BD Day 361/EoS. • Proportion of participants with seroresponse from baseline (defined as before primary dose) in RSV-binding Ab concentration up to BD Day 361/EoS. • Proportion of participants with ≥2-fold increase from baseline (defined as before primary dose) in RSV-binding Ab concentration up to BD Day 361/EoS. • Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

Abbreviations: Ab = antibody, AE = adverse event, AR = adverse reaction, AESI = adverse event of special interest, BD = booster dose, EoS = end of study, GMC = geometric mean concentration, GMFR = geometric mean fold rise, GMT = geometric mean titer, MAAE = medically attended adverse event, RSV = respiratory syncytial virus, SAE = serious adverse event.

4.3. Study Design

4.3.1. General Design (Part C)

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 (Table 11). The study schema is presented in Figure 3.

The study will enroll approximately 500 adults ≥50 years of age who are medically stable. The eligibility criteria are provided in Section 4.4. On BD Day 1, each participant will receive one IM injection of mRNA-1345 ([redacted] µg), administered into the deltoid muscle of either the right or left arm.

Participants will have scheduled visits and safety calls according to the timepoints specified in the SoA (Table 11). 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 (ie, 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.

Safety monitoring for this study will include the study team members inclusive of, at a minimum, the Sponsor's Medical Monitor and Safety Physician and a CRO Medical Monitor. The study team will conduct ongoing safety reviews during the study. This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

4.3.2. Scientific Rationale for Study Design

This study is designed as a single arm, open-label study to evaluate safety, tolerability, and immunogenicity of a BD of mRNA-1345 in adults ≥50 years of age who have previously received a primary dose of mRNA-1345. The mRNA-1345 recipients in the PP set in Part B (Group 4 [mRNA-1345 + placebo] and Group 5 [mRNA-1345 + mRNA-1273.214]) of this study who are willing to enroll in Part C will be screened accordingly. In Part C, eligible participants will receive mRNA-1345 boost at 1 Year following the primary dose (Table 11).

4.3.3. Choice of Vaccine Dose

The [redacted]-µg dose of mRNA-1345 was selected for this study based on the mRNA-1345-P101 study data (Section 1.1.6).

4.3.4. EoS Definition

A participant is considered to have completed the study if they have completed the last scheduled procedure on BD Day 361 (ie, 12 months after administration of mRNA-1345 on BD Day 1; Table 11). The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure, as shown in the SoA (Table 11).

4.4. Study Population (Part C)

Approximately 500 participants will be enrolled.

Note: Enrolled means participant agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

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

4.4.1. Inclusion Criteria (Part C)

Participants are eligible to be included in the study only if all the following criteria apply:

1. Participants at Part C study sites who have been enrolled in Part B (Groups 4 and 5) of this study; have immunogenicity blood sampling at Part B baseline and Day 29; completed the Day 211/EoS visits for Part B; were included in the PP set; and received 1 dose of mRNA-1345 at least 12 months (but no later than 15 months) prior to the time of enrollment.
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures, and is in general good health according to the Investigator's assessment.
3. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as bilateral tubal ligation >1 year prior to Screening, bilateral oophorectomy, hysterectomy, or menopause. An FSH level may be measured at the discretion of the Investigator to confirm menopausal status.
4. Female participants of childbearing potential may be enrolled in the study if the participant: (1) has a negative urine pregnancy test at Screening and on the day of injection, (2) has practiced adequate contraception or has abstained from all activities that could lead to pregnancy for 28 days prior to vaccination, (3) has agreed to continue adequate contraception through 3 months following the BD injection, and (4) is not currently breastfeeding.

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

   - Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide.
   - Intrauterine device.
   - Hormonal contraceptive in the form of a pill or patch.
   - Medroxyprogesterone injection (eg, Depo-Provera®).
   - Etonogestrel implant (eg, Nexplanon®).
   - Sterilization of a female participant's male partner prior to entry into the study.

– Vasectomy for male participants.

Note: Periodic abstinence (eg, calendar, ovulation, symptom-thermal, postovulation methods,) and withdrawal are not acceptable methods of contraception.

5. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
6. Able to comply with study requirements, including access to transportation for study visits.
7. Access to inbound and outbound telephone communication with caregivers and study staff.

4.4.2. Exclusion Criteria (Part C)

Participants are not eligible to be included in the study if any of the following criteria apply:

1. Participation in another interventional clinical research study where participant has received any IP (drug/biologic/device) within 6 months before the planned date of the BD Day 1 study injection. Any prior receipt of an investigational or approved vaccine against RSV, except as part of mRNA-1345 Study P302 Part B, is exclusionary.
2. Participant is acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to Screening Visit or BD Day 1. Participants meeting this criterion may be rescheduled within the 14-day Screening window and will retain their initially assigned participant number.
3. History of a diagnosis or condition, that in the judgment of the Investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication ≤60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

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

   Participants who have undergone surgical procedures within 7 days prior to BD Day 1 or are scheduled to undergo a surgical procedure within 28 days after study injection are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency; asplenia or recurrent infections; or an immunocompromizing/immunosuppressive condition that requires systemic treatment with immunosuppressive therapy, including cytotoxic agents, radiotherapy, or monoclonal antibodies for cancer or an autoimmune disorder with the following exceptions.
   a. Participants who are HIV positive with CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50 to

500 viral copies, which do not lead to changes in antiretroviral therapy) as determined from participant's medical records are permitted.

b. Certain immune-mediated conditions that are stable and well-controlled (eg, alopecia areata, Hashimoto thyroiditis, type 1 diabetes mellitus, gout, autoimmune ovarian failure) as well as those that do not require systemic immunosuppressants per Exclusion Criterion 5 (eg, asthma, psoriasis, or vitiligo) are permitted at the discretion of the Investigator.

5. Participants who received systemic immunosuppressants for >14 days in total within 180 days prior to BD Screening Visit (for glucocorticoids ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study (including intra-articular steroid injections). Inhaled, nasal, and topical steroids are allowed.
6. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
7. Any reported history of anaphylaxis or known immediate hypersensitivity to any component of the study product or any mRNA vaccine(s), including polyethylene glycol.
8. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
9. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
10. Known uncontrolled disorder of coagulation.
    Note: In the setting of well-controlled atrial fibrillation, prophylaxis for cardiovascular thromboembolism or stroke with the following medications are allowed: aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin.
11. Participant has received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to the study injection (BD Day 1) or plans to receive a vaccine authorized or approved by a local health agency within 28 days after the study injections.
12. History of a serious reaction to any prior vaccination or Guillain-Barré syndrome 6 weeks after any prior influenza immunization.
13. Receipt of systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study.
14. Participant has a history of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
15. Participant has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
16. Participant is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

4.4.3. Lifestyle Restrictions

Not applicable.

4.4.4. Screen Failures

See Section 2.4.4 for details.

4.5. Study Treatment

4.5.1. Investigational Products Administered

mRNA-1345 is an LNP-encapsulated mRNA-based vaccine consisting of mRNA encoding the RSV fusion glycoprotein stabilized in the prefusion conformation.

4.5.2. Randomization and Blinding

Not applicable.

4.5.2.1. Blinding

Not applicable.

4.5.2.2. Unblinding

Not applicable.

4.5.3. Preparation, Handling, Storage, and Accountability

4.5.3.1. Preparation of Study Vaccine

mRNA-1345 will be provided as a sterile liquid for injection and will be a white to off white dispersion at a concentration of CCI [redacted]

mRNA-1345 preparation instructions is detailed in the Pharmacy Manual.

4.5.3.2. Study Vaccine Administration

mRNA-1345 will be administered as one IM injection on BD Day 1 in the deltoid muscle, according to the procedures specified in the Pharmacy Manual. The arm (left or right) in which the injection is administered will be recorded by the site staff.

On BD Day 1, participants will be monitored for a minimum of 30 minutes after injection. Assessments will include, but are not limited to, vital sign measurements and monitoring for local or systemic ARs as shown in the SoA (Table 11).

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

4.5.3.3. Study Vaccine Delivery and Receipt

The Sponsor (or designee) is responsible for the following:

- Supplying mRNA-1345 to the study sites.
- Confirming the appropriate labeling of the IP so it complies with the legal requirements of the US.

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

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

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

4.5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the Investigator (via the study site pharmacy) with adequate quantities of the IP.

mRNA-1345 will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, the International Council for ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

4.5.3.5. Study Vaccine Storage

mRNA-1345 should be stored at –25ºC to –15ºC (–13ºF to 5ºF). mRNA-1345 must be received by a designated study personnel at the study site, handled and stored safely, kept in a secure location with restricted access, and protected from moisture and light until it is prepared for administration. Additional details are found in the Pharmacy Manual.

4.5.3.6. Study Vaccine Accountability

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

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

4.5.3.7. Study Vaccine Handling and Disposal

The study site monitor will reconcile the IP inventory during the conduct of the study and at the EoS for compliance. Once fully reconciled at the site at the EoS, the IP can be destroyed on-site,

if study site procedures allow, or returned to a destruction depot per instruction of the Sponsor. Additional details are found in the Pharmacy Manual.

4.5.4. Study Intervention Compliance

The IP will be administered at the study site under direct observation of medically qualified study personnel and appropriately recorded (date and time) in the source documents and eCRF. The qualified study personnel will confirm that the participant has received the entire dose of the IP, record the injection site (left or right deltoid) and corresponding IP administered. If a participant does not receive the IP or does not receive all of the planned dose, the reason for the missed dose will be recorded. The data will be reconciled with the study site accountability records to assess compliance.

The study site staff are responsible for ensuring that the participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete the visit within the defined visit window, as specified in the SoA (Table 11 [Part C]). If a participant does not complete a visit within the defined time window, that visit will be classified as a missed visit, and the participant will continue with the subsequent scheduled visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

4.5.5. Prior and Concomitant Medications

4.5.5.1. Prior Medications and Therapies

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

4.5.5.2. Concomitant Medications and Therapies

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

- All nonstudy vaccinations administered within the period starting 28 days before the study injection and through Month 12/EoS.
- All concomitant medications taken through 28 days after injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19, RSV, or any other infectious disease symptoms.
- Any concomitant medications relevant to or for the treatment of MAAE from BD Day 1 through Month 6.
- Any concomitant medications relevant to or for the treatment of SAE or AESI, from BD Day 1 through Month 12/EoS.

- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study site visits or via other participant interactions (eg, safety telephone calls).
- Use of facial injections or dermal fillers for cosmetic or medical indications such as migraine headaches.

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

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

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

See Section 2.5.5.3 for details.

4.5.6. Intervention After the End of the Study

See Section 2.5.6 for details.

4.6. Delay or Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

4.6.1. Criteria for Delay of Vaccine Administration

4.6.1.1. Individual Participant Criteria for Delay of Study Vaccination

See Section 2.6.1.1 for details and refer to the SoA for Part C (Table 11).

4.6.2. Participant Discontinuation/Withdrawal from the Study

See Section 2.6.2 for details.

4.6.3. Lost to Follow-Up

See Section 2.6.3 for details.

4.7. Study Assessments and Procedures

See Section 2.7 for details and refer to the SoA for Part C (Table 11).

4.7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 11 [Part C]):

- Solicited local and systemic ARs (Section 2.7.4.3) that occur during the 7 days following vaccine administration (ie, the day of study injections and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 4.7.1.1). Local solicited ARs will be recorded separately for each injection site.
- Unsolicited AEs observed or reported from the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 2.7.4.1 and Section 2.7.4.2.
- MAAEs from BD Day 1 through BD Day 181 (BD Month 6).
- SAEs, AESIs, and AEs leading to discontinuation from study participation from vaccination on Day 1 through BD Day 361/EoS or withdrawal from the study.
- Vital sign measurements (Section 2.7.1.3).
- Physical examination findings (Section 2.7.1.4).

The incidence and severity of the above events will be monitored by study team members inclusive of, at a minimum, the Sponsor's Medical Monitor and Safety Physician and a CRO Medical Monitor who will conduct ongoing safety reviews during the study.

4.7.1.1. Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary (for 7-day reactogenicity) using either an application downloaded to their smartphone or a device that will be provided at the time of enrollment. If the participant is unable to complete the eDiary on their own, a caregiver can assist with the data entry, but the information entered in the eDiary must come from the participant.

Before enrollment on BD Day 1, the participant will be instructed to download the eDiary application or will be provided with an eDiary device to record solicited ARs (Section 4.7.4.3). and to receive eDiary prompts.

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

On the injection day, participants will record data in the eDiary starting approximately 30 minutes after administration of the injection under supervision of the study site staff to ensure correct completion of the eDiary. The study site staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the study site once per day, preferably in the evening and at the same time each day, on the day of injection and 6 subsequent days.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 4.7.4.3, that occur on the day of injection and during the 7 days after injection (ie, the day of

injection and 6 subsequent days). Local solicited ARs will be recorded for the injection site. ARs beyond Day 7 should be reviewed either at the next scheduled study site visit or during the safety telephone call.

- Daily oral body temperature measurements should be performed using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Other measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) should be performed using the ruler provided by the study site.
- Whether any medications were taken to treat or prevent pain or fever on the day of injection and 6 subsequent days.

The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

If eDiary prompts result in identification of relevant safety events according to the study period, a follow-up safety contact will be triggered to determine whether an unscheduled visit should be arranged.

For Part C, the study site staff will review eDiary data with participants on BD Day 8 visit (Visit 2).

4.7.1.1.1 Ancillary Supplies for Participant Use

See Section 2.7.1.1.1 for details.

4.7.1.2. Safety Telephone Call

The safety telephone call will be made to the participants by trained study site personnel. This call will follow a Sponsor-approved script, which will facilitate the collection of relevant safety information. Safety telephone calls by the study site to each participant will occur at the timepoints indicated in the SoA (Table 11). The participant will be interviewed according to the script about the occurrence of AEs, MAAEs, AESIs, SAEs, AEs leading to discontinuation, concomitant medications associated with those events, and any nonstudy vaccinations (Section 2.7.4.6). All safety information collected from the telephone call must be documented in the source documents as described by the participant and not documented on the script used for the safety telephone call. As noted in Section 4.7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

4.7.1.3. Vital Sign Measurements

See Section 2.7.1.3 for details and refer to the SoA for Part C (Table 11).

4.7.1.4. Physical Examinations

See Section 2.7.1.4 for details and refer to the SoA for Part C (Table 11).

4.7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the timepoints indicated in the SoA (Table 11). Immunogenicity assessments will be performed for all participants. The following analytes will be measured:

- RSV-A and RSV-B nAbs measured by microneutralization assay.

Sample collection, handling, and volume will be provided in the lab manual. Unique sample identification will be used to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

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

According to the ICF (Section 6.1.6), excess serum from the blood samples collected for immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to RSV, other related respiratory viruses, and additional assay development.

4.7.3. Efficacy Assessments

Not applicable.

4.7.4. Safety Definitions and Related Procedures

4.7.4.1. Adverse Event

See Section 2.7.4.1 for details and refer to the SoA for Part C (Table 11).

4.7.4.2. Serious Adverse Events

See Section 2.7.4.2 for details and refer to the SoA for Part C (Table 11).

4.7.4.3. Solicited Adverse Reactions

See Section 2.7.4.3 for details and refer to the SoA for Part C (Table 11).

4.7.4.4. Medically Attended Adverse Events

See Section 2.7.4.4 for details.

4.7.4.5. Adverse Event of Special Interest

See Section 2.7.4.5 for details.

Investigators should report events listed in Table 14, Section 6.3.1 as an AESI for Part C.

4.7.4.6. Eliciting and Documenting Adverse Events

See Section 2.7.4.6 for details and refer to the SoA for Part C (Table 11).

4.7.4.7. Assessment of Intensity

See Section 2.7.4.7 for details and refer to the SoA for Part C (Table 11).

4.7.4.8. Assessment of Causality

See Section 2.7.4.8 for details and refer to the SoA for Part C (Table 11).

4.7.4.9. Reporting Adverse Events

See Section 2.7.4.9 for details and refer to the SoA for Part C (Table 11).

4.7.4.10. Reporting Serious Adverse Events

See Section 2.7.4.10 for details and refer to the SoA for Part C (Table 11).

4.7.4.11. Reporting of Adverse Events of Special Interest

See Section 2.7.4.11 for details and refer to the SoA for Part C (Table 11).

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

See Section 2.7.4.12 for details and refer to the SoA for Part C (Table 11).

4.7.4.13. Method of Detecting AEs and SAEs

See Section 2.7.4.13 for details and refer to the SoA for Part C (Table 11).

4.7.4.14. Follow-up of AEs and SAEs

See Section 2.7.4.14 for details and refer to the SoA for Part C (Table 11).

4.7.4.15. Regulatory Reporting Requirements for SAEs

See Section 2.7.4.15 for details and refer to the SoA for Part C (Table 11).

4.7.5. Pregnancy

See Section 2.7.5 for details and refer to the SoA for Part C (Table 11).

4.7.6. Safety Monitoring

Safety monitoring for this study will include study team members inclusive of, at a minimum, the Sponsor's Medical Monitor and Safety Physician and a CRO Medical Monitor. The study team will conduct ongoing safety reviews during the study.

4.7.7. Treatment of Overdose

See Section 2.7.7 for details.

4.7.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

4.7.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

4.7.10. Biomarkers

Immunogenicity assessments are described in Section 4.7.2. Biomarker assessment may include genomics and transcriptomics samples.

4.7.11. Health Economics

Health economics are not evaluated in this study.

4.8. Statistical Considerations

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

4.8.1. Blinding and Responsibility for Analyses

Not applicable.

4.8.1.1. Breaking the Blind

Not applicable.

4.8.2. Statistical Hypotheses

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.

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 (ie, 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.

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 (ie, 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.

4.8.3. Sample Size Determination

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%.

4.8.4. Analysis Sets

The analysis sets are described in Table 13.

Table 13: Analysis Sets for Part C

Set	Description
Enrolled Set	All participants who completed the informed consent of Part C.
Part C PP Set	Includes all participants who received planned BD of mRNA-1345, have preBD and at least 1 post-injection assessment of immunogenicity after a BD, complied with the immunogenicity testing schedule, and had no major protocol derivations that impact key or critical data. The Part C PP Set will be the primary population for the analysis of immunogenicity data.
Part C Solicited Safety Set	Includes all participants who received 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.
Part C Safety Set	Includes all participants who received any BD of mRNA-1345. The Part C Safety Set will be used for the analyses of safety data, except for solicited ARs.

Abbreviations: AR = adverse reaction; PP = per protocol.

4.8.5. Statistical Methods

4.8.5.1. Immunogenicity Analysis

Unless otherwise specified immunogenicity analysis for Part C will be based on the Part C PP Set.

The primary immune endpoints based on RSV-A nAbs at BD Day 29 will be presented by descriptive summary statistics, such as median, minimum, maximum, and 95% CI for GMT. GMR will also be estimated to compare the immune response at BD Day 29 with the response at Day 29 post primary dose (ie, the primary CCI µg of mRNA-1345). GMR will be calculated by back transforming the mean of paired difference of RSV-A 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 primary immune endpoints that are based on RSV-B nAbs at BD Day 29 will be presented by the same methods as the methods for the primary immune endpoints of RSV-A nAbs at BD Day 29.

SRR of RSV-A nAbs or RSV-B nAbs is defined as proportion of participants with postinjection titers ≥4 × LLOQ if baseline is < LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ. Baseline value is defined as the most recent nonmissing immune measurements collected before the mRNA-1345 primary dose. The difference and 95% CI of difference in the SRR at BD Day 29 versus the SRR at Day 29 post primary dose in the same participant will be estimated through a logistic model with repeated measure (via PROC GENMOD) in SAS.

GMT with 2-sided 95% CIs and GMFR with 2-sided 95% CIs at each postbaseline timepoint will be provided. The number and percentage of participants with seroresponse at each postbaseline timepoint will also be provided with 2-sided 95% CIs using the Clopper-Pearson method. The proportion of participants with at least a 2-fold increases in titers (relative to baseline) will also be provided at each postbaseline timepoint with the 2-sided 95% CI.

For summarizations of the GMT, GMFR, and GMR, the Ab titers reported as below the LLOQ will be replaced by 0.5 × LLOQ. Titers greater than the ULOQ will be replaced by ULOQ.

Descriptive statistics (including 95% CIs) for the immunogenicity endpoints may also be provided by initial vaccination group and/or by the age at enrollment (50 to 59 years, 60 to 74 years, and ≥75) in Part B.

4.8.5.2. Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, AEs leading to 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 system organ class and preferred term according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used in this study.

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 the injection group corresponding to the IP the participants actually received in Part B, unless otherwise specified.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7 days following BD Day 1 will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to discontinuation from study participation will be summarized. The number of events will also be summarized.

For all other safety parameters, descriptive summary statistics will be provided.

The number and percentage of participants who have vital signs results below or above the normal ranges will be summarized by timepoint.

4.8.5.3. Exploratory Analyses

The exploratory analyses may be conducted after database lock and will be described in the SAP.

4.8.6. Planned Analyses

One primary analysis and one final analysis will be conducted in this Part of the study. Further details can be found in the SAP.

4.8.6.1. Primary Analysis

The primary analysis of immunogenicity and safety will be performed after all Part C participants have completed the BD Day 29 Visit. All data relevant to the primary analysis through the BD Day 29 visit in all participants will be cleaned (ie, data that are as clean as possible) and a report may be generated.

4.8.6.2. Final Analysis

The final analysis of all endpoints will be performed after all participants have completed EoS visit. 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 EoS.

4.8.7. Multiplicity

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.

5. REFERENCES

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6. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

6.1. APPENDIX 1: Study Governance Considerations

6.1.1. Regulatory and Ethical Considerations

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

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

6.1.2. Study Monitoring

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

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor, the designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the

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

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

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

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

6.1.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

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

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

6.1.4. Financial Disclosure

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

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

6.1.5. Recruitment Procedures

Advertisements to be used for the recruitment of study participants and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

6.1.6. Informed Consent/Assent Process

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

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

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

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

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

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

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

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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 14 days from the previous ICF signature date (within the initial Screening period).

The ICF will also explain that excess serum from the blood samples collected for immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further understand the infection and disease associated with RSV and related viruses, including analyses related to the immunology of this vaccine, viral infection, and clinical conduct.

6.1.7. Protocol Amendments

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

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

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

6.1.8. Protocol Deviations

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

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

6.1.9. Data Protection

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

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

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

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

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

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

6.1.10. Sample Retention and Future Biomedical Research

The Sponsor may store samples for the time frame specified in the ICF to achieve the study objectives. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted, using other antibody-based methodologies, on any remaining blood or serum samples, including participants who provide samples for screening, but are not subsequently enrolled. These analyses would extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1345, as well as to determine how changes in the markers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

6.1.11. Safety Oversight

Safety monitoring for the study is described in Section 2.7.6, Section 3.7.6, and Section 4.7.6.

6.1.12. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov and the European Union Clinical Trials Register, as well as some national registries.

6.1.13. Data Quality Assurance and Quality Control

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

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period

without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

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

6.1.14. Data Collection and Management

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

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

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

AEs will be coded with MedDRA. Concomitant medications will be coded using WHO – Drug Global Dictionary.

6.1.15. Source Documents

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

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

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

6.1.16. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following

the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

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

6.1.17. Study and Site Closure

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

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

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

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

- Continuation of the study represents a significant medical risk to participants.
- Failure of the investigator to comply with the protocol, requirements of the IRB or local health authorities, Sponsor's procedures, or ICH GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further mRNA-1345 development.

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

6.1.18. Publication Policy

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

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

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

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

6.2. APPENDIX 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions: Woman of Child-bearing Potential

Women of child-bearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of mRNA-1345, an additional evaluation should be considered.

Women in the following categories are not considered women of child-bearing potential:

- Premenarchal
- Premenopausal, surgically sterile female with one of the following:
  - Documented complete hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

- Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and FSH levels in the postmenopausal range for the institution.
- Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiationinduced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants of child-bearing potential must be nonpregnant and nonlactating and meet the following criteria:

- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to vaccination and agrees to consistently use a highly effective method of contraception through 3 months after the last injection (eg, barrier method with spermicide, intrauterine device, injectable/implanted/oral hormonal methods). Female participants should also refrain from breastfeeding throughout this period.

Collection of Pregnancy Information

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The investigator will collect follow-up information on the participant and the child, even if the participant is discontinued from the study, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Spontaneous miscarriages, congenital anomaly, and/or birth defect abortion should be reported as SAEs.
- Any poststudy, pregnancy-related SAE considered reasonably related to mRNA-1345 by the investigator will be reported to the Sponsor as described in Section 4.7.4.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue mRNA-1345 and should be followed for safety and not withdrawn from the study.

6.3. APPENDIX 3: Adverse Events of Special Interest

6.3.1. AESIs for RSV and Influenza

Investigators should report all events that fall into the categories presented in Table 14 as an AESI per the reporting processes specified in Section 2.7.4.11. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and safety platform for emergency vaccines (Brighton Collaboration 2019).

Table 14: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts <150 × 10^9 cells per liter • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
New onset of or worsening of neurologic diseases	Neurologic diseases include the following: • Guillain-Barré Syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per protocol Section 2.7.4.5.1 • Follow the reporting procedures in protocol Section 4.7.4.9
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

6.3.2. AESIs for COVID (Part B only)

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

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

Table 15: AESIs for COVID

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

Medical Concept	Medical Concept Descriptions/Guidance
Anosmia, Ageusia	• New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology • DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	• Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) • DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	• New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	• Any event of appendicitis
Rhabdomyolysis	• New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome (ARDS)	• New onset of ARDS/respiratory failure due to acute inflammatory lung injury • DOES NOT INCLUDE nonspecific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	• New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (eg. stroke, deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation)
Acute cardiovascular injury	• New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by electrocardiogram (eg. atrial fibrillation, atrial flutter, supraventricular tachycardia); stress cardiomyopathy; heart failure; acute coronary syndrome; myocardial infarction). • DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc.; • Increase in serum creatinine by ≥0.3 mg/dl (or ≥26.5 µmol/l) within 48 hours; **OR** • Increase in serum creatinine to ≥1.5 ×baseline, known or presumed to have occurred within prior 7 days.

Medical Concept	Medical Concept Descriptions/Guidance
Acute liver injury	• New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.: • >3-fold elevation above the upper normal limit for ALT or AST; **OR** • >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single-organ cutaneous vasculitis • Erythema multiforme • Bullous rash • Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms, fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	• Multisystem inflammatory syndrome in adults or children • Kawasaki's disease • Hemophagocytic lymphohistiocytosis
Thrombocytopenia	• Platelet count $<150 \times 10^9$/L (thrombocytopenia) • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or hemolysis, elevated liver enzymes, and low platelet count syndrome
Acute aseptic arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or polymerase chain reaction. • DOES NOT INCLUDE new onset of chronic arthritic conditions

New onset, or worsening, of neurological disease	• Immune-mediated neurological disorders
	  • Guillain-Barré Syndrome
	  • Acute disseminated encephalomyelitis
	  • Peripheral facial nerve palsy (Bell's palsy)
	  • Transverse myelitis
	  • Encephalitis/encephalomyelitis
	  • Aseptic meningitis
	  • Seizures/convulsions/epilepsy
	  • Narcolepsy/hypersomnia

Anaphylaxis	• Anaphylaxis associated with study drug administration

Medical Concept	Medical Concept Descriptions/Guidance
Other syndromes	• Fibromyalgia • Postural orthostatic tachycardia syndrome • Chronic fatigue syndrome • Myalgic encephalomyelitis • Postviral fatigue syndrome • Myasthenia gravis

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

The CDC working case definition of pericarditis, myocarditis, and myopericarditis to be used in this study is presented in Table 16.

Table 16: CDC Working Case Definition of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Condition	Definition	
Acute myocarditis	**Probable Case**	**Confirmed Case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms[a]	Presence of ≥ 1 new or worsening of the following clinical symptoms[a]
	• Chest pain, pressure, or discomfort.	• Chest pain, pressure, or discomfort.
	• Dyspnea, shortness of breath, or pain with breathing.	• Dyspnea, shortness of breath, or pain with breathing.
	• Palpitations.	• Palpitations.
	• Syncope.	• Syncope.
	OR, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:	**OR,** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:
	• Irritability.	• Irritability.
	• Vomiting.	• Vomiting.
	• Poor feeding.	• Poor feeding.
	• Pachypnea.	• Tachypnea.
	• Lethargy.	• Lethargy.
	AND	**AND**
	≥ 1 new finding of	≥ 1 new finding of
	• Troponin level above the upper limit of normal (any type of troponin).	• Histopathologic confirmation of myocarditis[b].
	• Abnormal ECG or rhythm monitoring findings consistent with myocarditis[c].	
	• Abnormal cardiac function or wall motion abnormalities on an echocardiogram.	• cMRI findings consistent with myocarditis in the presence of a troponin level above the upper

Condition	Definition	
	• cMRI findings consistent with myocarditis.	limit of normal (any type of troponin).
	AND	**AND**
	• No other identifiable cause of the symptoms and findings.	• No other identifiable cause of the symptoms and findings.
Acute pericarditis[d]	Presence of ≥2 new or worsening of the following clinical features:	
	• Acute chest pain.	
	• Pericardial rub on examination.	
	• New ST-elevation or PR-depression on ECG.	
	• New or worsening pericardial effusion on echocardiogram or magnetic resonance imaging.	
Myopericarditis	This term may be used for participants who meet the criteria for both myocarditis and pericarditis.	

Abbreviations: AV = atrioventricular; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram.

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

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

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

c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

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

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

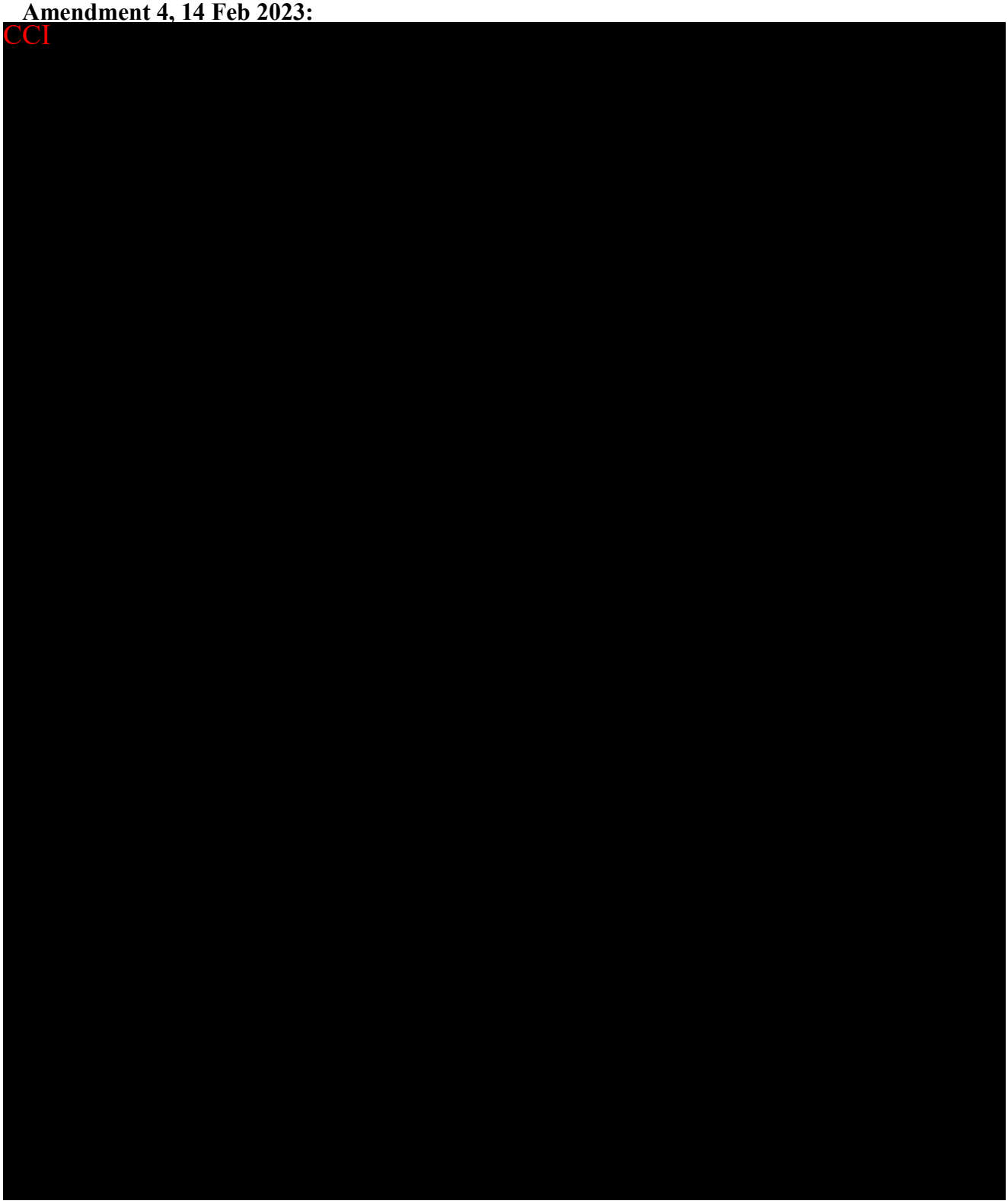
Source: Gargano et al 2021.

6.5. APPENDIX 5: Protocol Amendment History

6.5.1. Protocol Amendment 4

Amendment 4, 14 Feb 2023:

CCI



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[redacted]

6.5.2. Protocol Amendment 3

Amendment 3, 17 June 2022:

CCI

[redacted]

CCI

[redacted]

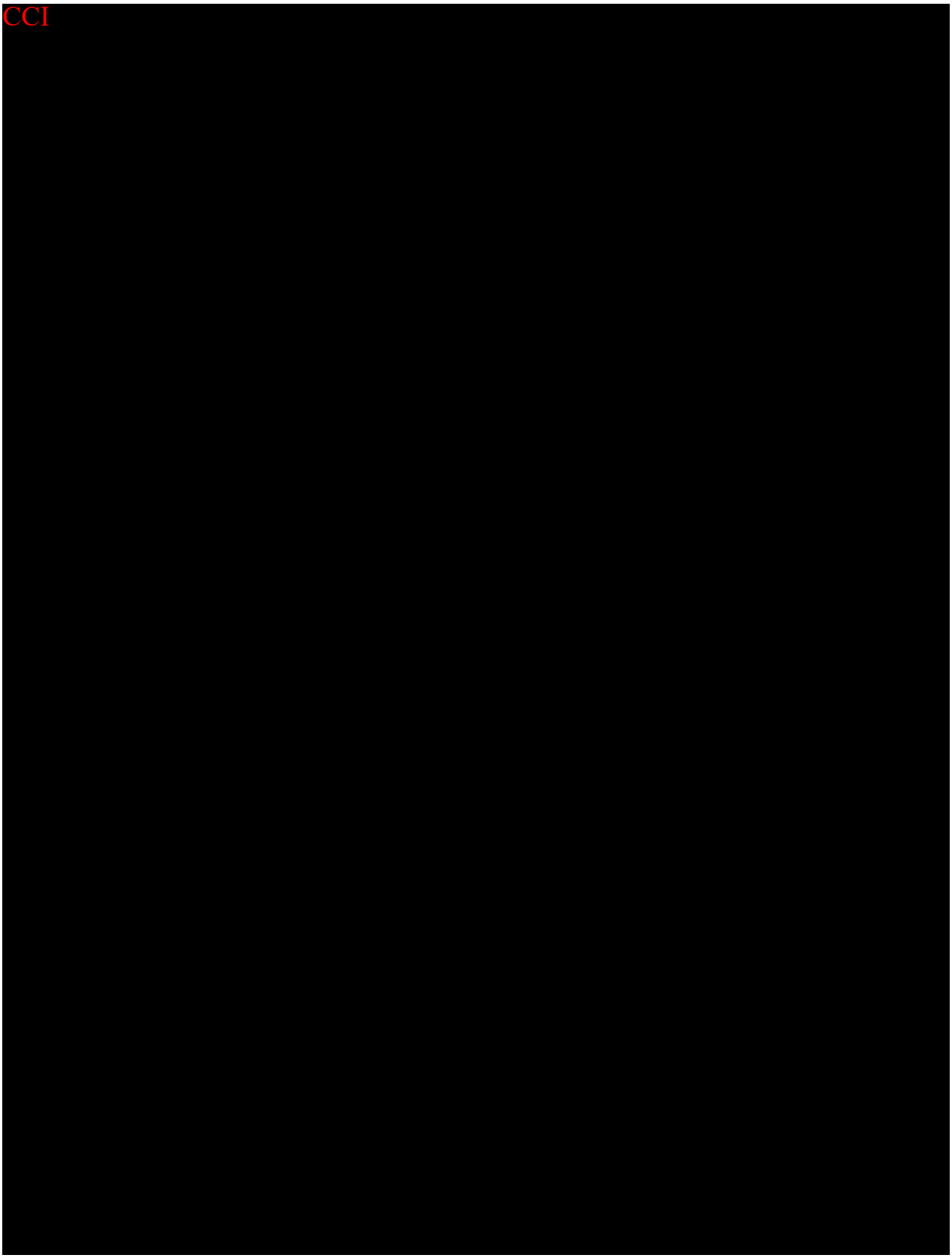
6.5.3. Protocol Amendment 2

Amendment 2, 10 May 2022:

CCI

[redacted]

CCI



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6.5.4. Protocol Amendment 1

Amendment 1, 17 Mar 2022:

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2nd Approval	PPD (Moderna) Medical 23-Jun-2023 18:16:49 GMT+0000

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