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, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age
Protocol Number:	mRNA-1345-P304
Date:	11 JUL 2023
Compound:	mRNA-1345
Brief Title:	A Study to Investigate the Safety and Immune Response of mRNA-1345, an mRNA Vaccine Targeting RSV, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age
Study Phase:	3
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number:	**Registry:** IND **ID:** 23342

Sponsor Signatory:

See e-Signature and date signed on last page the document.

Sponsor Signatory and Contact Information will be provided separately.

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, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age" dated 11 JUL 2023 and the most recent version of the mRNA-1345 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 local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB/IEC 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 Subinvestigator. 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 staff and members of the IRB/IEC. 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, regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
bAb	Binding antibody
CD	Clusters of differentiation
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
cMRI	Cardiac magnetic resonance imaging
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
ECG (or EKG)	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data collection
eDiary	Electronic Diary
EoS	End of study
FAS	Full analysis set
FluSurv-NET	Influenza Hospitalization Surveillance Network
GCP	Good Clinical Practices
GLSM	Geometric least square mean
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMR	Geometric mean titer ratio
GMT	Geometric mean titer
HA	Hemagglutination
HAI	Hemagglutination inhibition
HD	High dose

Abbreviation	Definition
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular
IRB	Institutional Review Board
IST	Internal safety team
IVRS	Interactive voice response system
IWRS	Interactive web response system
LB	Lower bound
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LRTD	Lower respiratory tract disease
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibody
NH	Northern Hemisphere
OTC	Over-the-counter
PP	Per protocol
QTL	Quality tolerance limit
RSV	Respiratory Syncytial Virus
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Safety telephone call
SCR	Seroconversion rate
SH	Southern Hemisphere

Abbreviation	Definition
SoA	Schedule of Activities
SRR	Seroresponse rate
ULOQ	Upper limit of quantification
USV	Unscheduled visit
V	In-person visit
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

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, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age

Brief Title:

A Study to Investigate the Safety and Immune Response of mRNA-1345, an mRNA Vaccine Targeting RSV, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age

Regulatory Agency Identifier Number(s):

Registry	ID
IND	23342

Rationale:

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 people at risk for both RSV and influenza diseases.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone® HD).	• Solicited local and systemic ARs through 7 days after each injection. • Unsolicited AEs through 21 days after each study injection. • MAAEs from Day 1 to Month 6 after last study injection/EoS. • AESI from Day 1 to Month 6 after last study injection/EoS. • SAEs from Day 1 to Month 6 after last study injection/EoS. • AEs leading to discontinuation from Day 1 to Month 6 after last study injection/EoS.
• To evaluate the impact of coadministered HD quadrivalent seasonal influenza vaccine on the immune response to mRNA-1345 RSV vaccine against RSV-A and RSV-B.	• GMT of serum RSV-A and RSV-B nAbs at Day 22 (Arm 1 [a]) or Day 43 (Arm 2 [b]).

Objectives	Endpoints
• To evaluate the impact of coadministered mRNA-1345 RSV vaccine on the immune response to HD quadrivalent seasonal influenza vaccine against 4 vaccine-matched influenza A and B strains.	• GMT of serum anti-HA Ab level as measured by HAI assay at Day 22.
Secondary	
• To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response to RSV-A and RSV-B.	• SRR[c] for RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2). • GMFR of postinjection RSV-A and RSV-B nAbs (Day 22 for Arm 1 and Day 43 for Arm 2) compared to baseline (Day 1 for Arm 1 and Day 22 for Arm 2). • Proportion of participants with ≥2-fold increase in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2).
• To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response against 4 vaccine-matched influenza A and B strains.	• SCR[d] at Day 22 as measured by HAI assay. • GMFR comparing Day 1 (baseline) and Day 22 measured by HAI assay.
Exploratory (may be performed)	
• To further evaluate the immune response across study vaccines.	• GMC and GMFR of postinjection/baseline titers of RSV bAbs. • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV bAb concentration postinjection. • Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses.

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; EoS = end of study; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; HAI = hemagglutination inhibition; HD = high dose; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; RSV = respiratory syncytial virus; SAE = serious adverse event; SCR = seroconversion rate; SRR = seroresponse rate.

a. Arm 1: Fluzone HD+mRNA-1345 [redacted] µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22.
b. Arm 2: Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 [redacted] µg on Day 22.
c. Seroresponse is defined as postvaccination titers ≥4×LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ.
d. Seroconversion is defined as postvaccination titer ≥1:40 if baseline is <1:10 or a ≥4-fold rise in postvaccination HAI Ab titer if baseline is ≥1:10.

Overall Design Synopsis:

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 sequentially

(3 weeks apart) or coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD) in adults ≥65 years of age.

All participants will participate in a Screening period (up to 28 days before Day 1), Intervention period (vaccine[s] and/or placebo administration on Day 1 and Day 22), and a Follow-up period (up to 7 months).

The study will enroll approximately 1900 medically stable adults ≥65 years of age. On Day 1, each participant will receive 2 injections, one in each arm. On Day 22, each participant will receive 1 injection. All injections will be administered IM, in the deltoid muscle. Participants will be randomized to study arms as shown in the schema (Section 1.2) to receive either 1) Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22; or 2) Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22.

Randomization will be stratified by age (65 to <75 years and ≥75 years [approximately 10%]).

Brief Summary:

The study aims to evaluate the safety and reactogenicity of mRNA-1345 RSV vaccine when coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD) in adults ≥65 years of age. The study will examine the impact of Fluzone HD on the immune response to mRNA-1345 against RSV-A and RSV-B, as well as the impact of mRNA-1345 on the immune response against 4 vaccine-matched influenza A and B strains.

Study details include:

- There will be 4in-person visits and 4 safety calls (see the SoA [Table 1]).
- All participants will be asked to complete an eDiary for solicited local and systemic ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days) after dosing on Day 1 and Day 22.
- Detection of unsolicited AEs will be through 21 days after each study intervention dosing (ie, the day of study intervention dosing and 20 subsequent days). Detection of MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Month 6 after the last study injection (EoS) or withdrawal from the study.

Number of Participants:

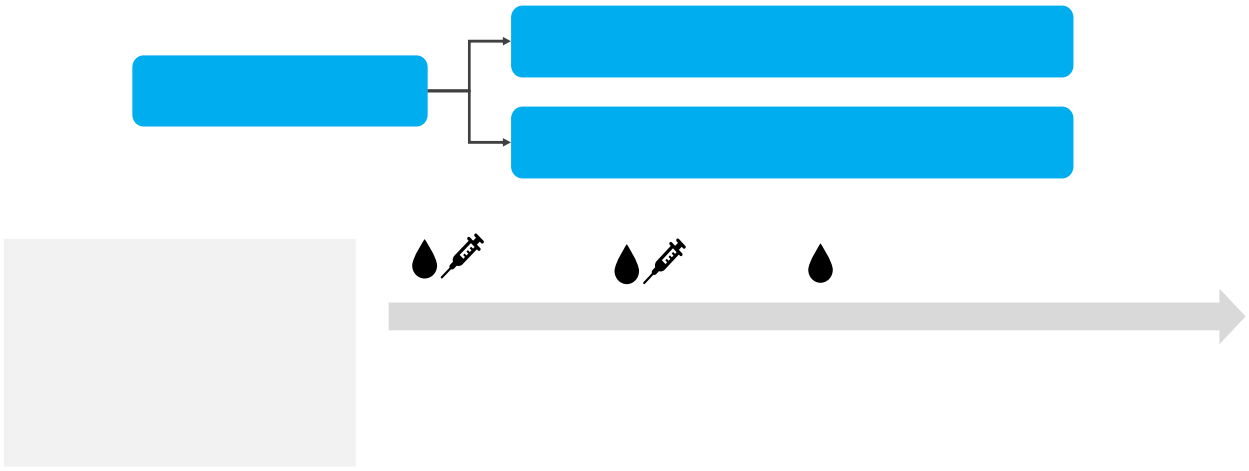
Approximately 1900 participants will be randomized in a 1:1 ratio to the assigned study interventions.

Study Arms and Duration:

- The study will be composed of 2 study arms.
- The total duration of the study participation is up to approximately 8 months from the Screening Visit.

1.2. Schema

Figure 1: Study Schema



Abbreviations: EoS = end of study; HD = high dose; N = number of participants.
Note: A blood sample will be drawn at each in-person visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Period	**Screening**	**Intervention Period**			**Follow-up**			
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Month*	**-1**	**1**	**1**	**1**	**1**	**2**	**3**	**6**
Visit Day	**Screening[a]**	**D1[a]**	**D8**	**D22**	**D29**	**D43[b]**	**D91**	**D202/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**+7**	**+3**	**-2 to +7**	**±5**	**±14**
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**V**	**SC**	**SC**
Informed consent, demographics, concomitant medications and vaccinations, and medical history	X	–	–	–	–	–	–	–
Inclusion/exclusion criteria	X	X	–	–	–	–	–	–
Physical examination[c]	X	X	–	X	–	–	–	–
Vital sign measurements[d]	X	X	–	X	–	–	–	–
Randomization	–	X	–	–	–	–	–	–
Blood sample collection for humoral immunogenicity[e]	–	X	–	X	–	X	–	–
Study vaccination (including a 30-minute postdose observation period)[d,f]	–	X	–	X	–	–	–	–
eDiary activation for recording solicited ARs (7 days)[g]	–	X	–	X	–	–	–	–
eDiary review[g]		X	X	X	X			
Follow-up safety telephone call[h]	–	–	X	–	X	–	X	X
Recording of unsolicited AEs	–	X	X	X	X	X	–	–
Concomitant medications[i]	–	X	X	X	X	X	–	–
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[h]	–	X	X	X	X	X	X	X

Study Period	**Screening**	**Intervention Period**			**Follow-up**			
Visit Number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Month*	**-1**	**1**	**1**	**1**	**1**	**2**	**3**	**6**
Visit Day	**Screening[a]**	**D1[a]**	**D8**	**D22**	**D29**	**D43[b]**	**D91**	**D202/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**+7**	**+3**	**-2 to +7**	**±5**	**±14**
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**V**	**SC**	**SC**
Recording of nonstudy vaccinations[h,i]	–	X	X	X	X	X	X	X
Study completion	–	–	–	–	–	–	–	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; D = Day; eDiary = electronic diary; EoS = end of study; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; RSV = respiratory syncytial virus; SAE = serious adverse event; SC = safety telephone call; ; V = in-person visit; – = indicated activity not performed on that day.

*A month is defined as 30 days.

Arm 1: Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22;

Arm 2: Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22.

a. The Screening Visit and Day 1 Visit may be performed on the same day or on different days (see Section 5.3 for additional details).

b. If a participant cannot attend a scheduled in-person visit (with the exception of the Screening Visit, Day 1, and Day 22), a home visit is acceptable if performed by appropriately delegated study clinic staff.

c. A complete 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 (see Section 8.3.1 for additional details).

d. Vital sign measurements include assessment of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (preferred route is oral) (see Section 8.3.2 for additional details).

e. Blood samples for humoral immunogenicity must be collected prior to administration of the study intervention on Day 1 and Day 22.

f. All participants will be randomized to receive 2 IM injections, one in each arm, in the deltoid muscle (Day 1) and 1 IM injection in the deltoid muscle (Day 22).

g. At Day 1 and Day 22, eDiary instruction will be provided while the participant is onsite. The participant will be required to make eDiary entries approximately 30 minutes after each vaccination while at the study site and again that same evening when at home. Study participants will continue to record in the eDiary each day at the same time for 6 days following each vaccination. Local solicited ARs will be recorded separately for each injection. eDiary review by the site should occur daily on Day 1-Day 7 and Day 22-28. Additional review of the eDiary will occur at Day 8 and Day 29 between the site and the participant during the safety telephone calls.

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 21 days postvaccination for either RSV or influenza, and the occurrence of MAAEs, 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.

[i] All concomitant medications and procedures will be recorded for 21 days following each vaccination (Day 1 through Day 43); 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 Month 6 after the last study injection/EoS.

2. INTRODUCTION

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 2005; 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 IgA are risk factors for RSV infection, including more severe disease (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 (Crank et al 2019; Kurzweil et al 2013; Looney et al 2002). Therefore, RSV remains a significant unmet medical need.

The fusion glycoprotein of the RSV envelope is a conserved target of protective nAbs for both serotypes of RSV: RSV-A and RSV-B. ModernaTX, Inc. (the Sponsor) has developed a rapid-response, proprietary vaccine platform based on a mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The mRNA-1345 vaccine encodes for the RSV fusion glycoprotein that is stabilized in the prefusion conformation.

Seasonal influenza viruses are estimated by the WHO to cause 3 million to 5 million cases of severe illness and up to 650,000 deaths each year resulting in a challenge to public health (WHO 2023). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in both the NH and 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 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 and Loeb, 2021). 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% CI: 1.15 to 1.34 million) in older adults across 195 countries in 2015 (GBD 2015). An analysis of the US FluSurv-NET showed that hospitalization rates among adults aged 75 to 84 years and ≥85 years were 1.4 to 3.0 and 2.2 to 6.4 times greater, respectively, than rates for adults aged 65 to 74 years. In-hospital death or transfer to hospice occurred in 3.8% of patients aged 65 to 74 years, 5.3% of patients aged 75 to 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 to 223.5 per 100,000) (Graham 2019).

Because of increased morbidity and mortality associated with influenza infections in older adults, Fluzone HD Quadrivalent vaccine is one of 3 influenza vaccines (along with Flublok® Quadrivalent and Fluad® Quadrivalent) that is preferentially recommended for people 65 years and older. This preferential recommendation is new for the 2022-2023 season.

2.1. Study Rationale

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 people at risk for both RSV and influenza diseases.

2.2. Background

The Sponsor is using its mRNA-based platform to develop a custom manufactured LNP-encapsulated, mRNA-based vaccine to prevent disease associated with RSV infection. The vaccines included in this clinical study are described below.

mRNA-1345

mRNA-1345 is an 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, prefusion and postfusion. The prefusion state facilitates entry into the host cell through a conformational change to the postfusion state. The prefusion conformation was selected because it displays all the epitopes known to elicit nAb and is the primary target of the nAb response following RSV infection (Crank et al 2019; Graham 2019; McLellan et al 2013; Ngwuta et al 2015).

The mRNA-1345 vaccine is currently being evaluated in older adults for safety, reactogenicity, immunogenicity, or efficacy in 2 Phase 1 studies (mRNA-1345-P101, NCT04528719 and mRNA-1230-P101, NCT05585632), a Phase 1b open-label study (mRNA-CRID-001, NCT05397223), a Phase 2/3 study (mRNA-1345-P301, NCT05127434), and a Phase 3 study (mRNA-1345-P302, NCT05330975).

At the time of the 30 Nov 2022 data cutoff date for the Phase 2/3 study (mRNA-1345-P301, NCT05127434), the mRNA-1345 vaccine administered as a single [redacted] µg dose demonstrated an acceptable reactogenicity profile and no new safety concerns were identified in the study population of adults ≥60 years of age. Solicited local and systemic ARs were reported at higher rates in the mRNA-1345 group than in the placebo group. Most solicited ARs were Grade 1 or 2 in severity, occurred within 1 to 2 days after injection, and resolved within 1 to 2 days after onset. The most commonly reported solicited local AR was injection site pain. The most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. Fever was the only solicited AR to be reported as Grade 4, and reporting was balanced between the groups. Primary vaccine efficacy against RSV-confirmed LRTD was demonstrated with 83.7% (95.88% CI, 66.0, 92.2; p<0.0001) protection against RSV-LRTD with ≥2 symptoms and 82.4% (96.36% CI, 34.8, 95.3; p=0.0078) against RSV-LRTD with ≥3 symptoms.

Licensed HD Influenza Vaccine (Fluzone HD Quadrivalent)

Fluzone HD Quadrivalent is a vaccine manufactured by Sanofi Pasteur Inc. and is indicated for active immunization for the prevention of influenza disease caused by influenza A subtype

viruses and type B viruses contained in the vaccine. Fluzone HD Quadrivalent is indicated for use in persons ≥65 years of age.

Fluzone HD Quadrivalent is a 4-component flu vaccine containing CCI µg of HAs, and is supplied in prefilled syringes, CCI mL. Additional details about the vaccine are available in the package insert (Fluzone® HD Quadrivalent package insert, 2023).

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

There are no important identified risks currently identified for mRNA-1345.

IM vaccination commonly precipitates a transient, dose-dependent, and self-limiting local inflammatory reaction. Systemic ARs may also occur after vaccination.

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.

IM 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 AEs 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.

In the postauthorization 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).

2.3.2. Benefit Assessment

Participants who receive mRNA-1345 may or may not directly benefit from the vaccination. In a Phase 3 pivotal efficacy trial (mRNA-1345-P301, NCT05127434), the primary efficacy endpoint demonstrating vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2; $p<0.0001$) against RSV-LRTD as defined by 2 or more symptoms was achieved for mRNA-1345.

Participants will be contributing to the process of developing a new potentially prophylactic measure in an area of unmet medical need.

2.3.3. 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 and an IST to evaluate the safety and treatment status of all participants. An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis (see additional details in Section 8.4.7.2).

Considering the safety and efficacy data for mRNA-1345 to date, the Sponsor considers the potential benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD).	• Solicited local and systemic ARs through 7 days after each injection. • Unsolicited AEs through 21 days after each study injection. • MAAEs from Day 1 to Month 6 after last study injection/EoS. • AESI from Day 1 to Month 6 after last study injection/EoS. • SAEs from Day 1 to Month 6 after last study injection/EoS. • AEs leading to discontinuation from Day 1 to Month 6 after last study injection/EoS.
• To evaluate the impact of coadministered HD quadrivalent seasonal influenza vaccine on the immune response to mRNA-1345 RSV vaccine against RSV-A and RSV-B.	• GMT of serum RSV-A and RSV-B nAbs at Day 22 (Arm 1 [a]) or Day 43 (Arm 2 [b]).
• To evaluate the impact of coadministered mRNA-1345 RSV vaccine on the immune response to HD quadrivalent seasonal influenza vaccine against 4 vaccine-matched influenza A and B strains.	• GMT of serum anti-HA Ab level as measured by HAI assay at Day 22.
Secondary	
• To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response to RSV-A and RSV-B.	• SRR [c] in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2). • GMFR of postinjection RSV-A and RSV-B nAbs (Day 22 for Arm 1 and Day 43 for Arm 2) compared to baseline (Day 1 for Arm 1 and Day 22 for Arm 2). • Proportion of participants with ≥2-fold increase in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2).

Objectives	Endpoints
• To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response against 4 vaccine-matched influenza A and B strains.	• SCR [d] at Day 22 as measured by HAI assay. • GMFR comparing Day 1 (baseline) and Day 22 measured by HAI assay.
Exploratory (may be performed)	
• To further evaluate the immune response across study vaccines.	• GMC and GMFR of postinjection/baseline titers of RSV bAbs. • Proportion of participants with ≥2-fold and ≥4-fold increases in RSV bAb concentration postinjection. • Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses.

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end of study; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; HAI = hemagglutination inhibition; HD = high dose; LLOQ = lower limit of quantification; nAb = neutralizing antibody; RSV = respiratory syncytial virus; SAE = serious adverse event; SCR = seroconversion rate; SRR = seroresponse rate.

a. Arm 1: Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22.
b. Arm 2: Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22.
c. SRR is defined as postvaccination titers ≥4× LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ.
d. SCR is defined as postvaccination titer ≥1:40 if baseline is <1:10 or a ≥4-fold rise in postvaccination HAI Ab titer if baseline is ≥1:10.

4. STUDY DESIGN

4.1. Overall Design

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 sequentially (3 weeks apart) or coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD) in adults ≥65 years of age.

All participants will participate in a Screening period (up to 28 days before Day 1), Intervention period (vaccine[s] and/or placebo administration on Day 1 and Day 22), and a Follow-up period (up to 7 months).

The study will enroll approximately 1900 medically stable adults ≥65 years of age. On Day 1, each participant will receive 2 injections, one in each arm. On Day 22, each participant will receive 1 injection. All injections will be administered IM, in the deltoid muscle. Participants will be randomized to study arms as shown in Table 4 to receive either 1) Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22 (Arm 1); or 2) Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22 (Arm 2).

4.2. Scientific Rationale for Study Design

The mRNA-1345-P304 study will evaluate the safety and immunogenicity of mRNA-1345 CCI µg when coadministered with a commercial influenza vaccine (Fluzone HD) and compare it with administration of Fluzone HD followed by mRNA-1345 21 days later in medically stable older adults ≥65 years of age. This is a randomized, observer-blinded study.

In this study, only participants ≥65 years of age were considered due to the preferentially recommended influenza Fluzone HD Quadrivalent vaccine and the Sponsor's position 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 people at risk for both RSV and influenza diseases, further described in Section 2. Justification for Dose

Participants will receive 1 dose of mRNA-1345 CCI µg administered on either Day 1 or Day 22 (refer to Table 3). The CCI µg dose was chosen based on the observed reactogenicity and immunogenicity profiles in clinical Phase 1, 2, and 3 studies conducted with mRNA-1345.

Selected dose level for the Phase 2/3 study in adults ≥60 years: Based on the Study mRNA-1345-P101 Phase 1 data in adults aged 65 to 79 years, a single CCI µg injection was selected to be evaluated in the mRNA-1345-P301 Phase 2/3 pivotal efficacy and safety study, based on an optimal combination of an acceptable safety profile and boosting and persistence of RSV nAb titers. At the CCI µg dose level, the reported rate of any local or systemic solicited AR was 72.3%, with injection site pain the most commonly reported (65.9%). Most of the participants reporting any solicited AR at this dose level experienced mild, Grade 1 severity (59.6%), with lower rates of moderate, Grade 2 severity (6.4%) observed. In comparison, the reported rate of any local or systemic solicited AR in the placebo group was 45.5%.

Results from a prespecified interim analysis of the ongoing pivotal efficacy and safety study in adults ≥60 years of age, mRNA-1345-P301 (Section 2.2), demonstrate that the primary efficacy objectives were met, including:

- Vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD, defined by ≥2 symptoms and 82.4% (96.36% CI: 34.8, 95.3), defined by ≥3symptoms.
- mRNA-1345 was generally well tolerated, with no safety concerns identified.

4.3. End of Study Definition

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

A participant is considered to have completed the study if he or she has completed all periods of the study, including the last visit or scheduled procedure as shown in the SoA (Table 1).

5. STUDY POPULATION

5.1. Inclusion Criteria

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

Age

1. Adults ≥65 years of age, at the time of signing informed consent (Screening Visit or the day of the Randomization Visit).

Type of Participant and Disease Characteristics

2. Participants may have one or more chronic medical diagnoses, but should be medically stable as assessed by:
   - Absence of changes in medical therapy within 60 days of Day 1 due to treatment failure or toxicity,
   - Absence of serious or significant medical events within 30 days of 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.

Sex and Contraceptive/Barrier Requirements

3. A participant assigned female at birth is eligible to participate if they are postmenopausal or not a person of childbearing potential.

Informed Consent

4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol (see Section 10.1.3).

Other Inclusion Criteria

5. Investigator assessment that participant understands and is willing to comply with protocol-mandated follow-up, including all procedures and eDiary completion.
6. Access to inbound and outbound telephone communication with caregivers and study staff.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to or at Day 1.
2. Close contact with someone with laboratory-confirmed influenza and/or RSV infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu®) within the past 5 days prior to Day 1.

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 within 60 days prior to Day 1 and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
    - Asymptomatic conditions and conditions with no clinically significant 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, due to 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 each study intervention or are scheduled to undergo a surgical procedure within 21 days after each study intervention dosing 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, immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Participants who are HIV positive and on antiviral therapy with CD4 count $\geq$350 cells/mm^3 and HIV RNA $\leq$500 copies/mL within the past 12 months.
    - Participants with immune-mediated diseases which are stable (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or autoimmune ovarian failure, which do not require systemic immunosuppressants per Exclusion Criterion #14.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos; psoriasis patches affecting skin over the deltoid areas).
6. Participant has tested positive for influenza or RSV by local health authority-approved testing methods $\leq$6 months prior to Day 1.
7. History of myocarditis, pericarditis, or myopericarditis within 6 months prior to Day 1. Participants who have not returned to baseline after their convalescent period will also be excluded.
8. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or commercially available influenza vaccines and any components of the mRNA-1345 vaccine or commercially available influenza vaccines.
9. History of Guillain-Barré syndrome.
10. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.

11. History of malignancy within previous 5 years (excluding nonmelanoma skin cancer).
12. 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.
13. Any history of dementia or any medical condition that moderately or severely impairs cognition. (Note: if deemed necessary for clinical evaluation, the Investigator can use tools such as the Mini-Mental State Examination, Mini-Cog, or Montreal Cognitive Assessment to determine cognition levels of the participant).

Prior/Concomitant Therapy

14. Received systemic immunosuppressants for >14 days in total within 6 months prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, ophthalmic, and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study intervention dosing.
15. Participant has received systemic Igs or blood products within 90 days prior to Day 1 or plans to receive systemic Igs or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to Day 1, or plan to receive them, are also excluded.
16. 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 and Day 22) or plans to receive a vaccine authorized or approved by a local health agency within 28 days after study injections.
17. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine ≤6 months prior to Day 1.
18. Participant has received any RSV vaccine (authorized/approved by local health agency or investigational) prior to Day 1.
19. Participant is not aware whether they have received an influenza vaccine in the most recent influenza season (in the prior 12 months).
20. Participant has been treated with antiviral therapies for influenza (eg, Tamiflu) within 6 months prior to Day 1.

Prior/Concurrent Clinical Study Experience

21. Participated in an interventional clinical study within 28 days prior to the Day 1 Visit based on the medical history interview or plans to do so while participating in this study. Participants may continue in prior interventional study follow-up activities, as long as it does not involve further investigational treatment other than the study intervention described in this protocol (Note: interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary).

Other Exclusion Criteria

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. Participant is working or has worked as study personnel or is an immediate family member or household member of study personnel, study clinic staff, or Sponsor personnel.

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

5.4. Criteria for Temporarily Delaying the Administration of Study Intervention

Body temperature (oral preferred) must be measured on the study intervention visit before dosing. The following events constitute criteria for delay of study intervention dosing, and if any of these events occur at the time scheduled for dosing, the participant may receive the study intervention dosing at a later date within the time window specified in the SoA (Table 1), or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7):

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

Participants may be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the Investigator determines that the participant's health on the day of dosing temporarily precludes study intervention, the visit should be rescheduled within the allowed interval for that visit.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Interventions Administered

Fluzone HD and mRNA-1345 (Study Arm 1) or Fluzone HD and placebo (Study Arm 2) will be administered as IM injections, one in each deltoid muscle on Day 1, according to the procedures specified in the Pharmacy Manual. On Day 22, placebo (Study Arm 1) or mRNA-1345 (Study Arm 2) will be administered as an IM injection into the deltoid muscle, as specified in the Pharmacy Manual. The arm (left and/or right) will not be documented in a way that identifies in which arm that the vaccine or placebo has been administered. It will be recorded by the unblinded clinic staff who will keep the specifics confidential from other study documents/blinded personnel before unblinding is authorized.

Participants will be monitored for a minimum of 30 minutes after administration of the study intervention. Assessments will include vital sign measurements and monitoring for solicited ARs as shown in the SoA (Table 1).

Further instructions for the preparation and administration of mRNA-1345 are described in the Pharmacy Manual.

The study interventions administered are listed in Table 3.

Table 3: Study Interventions Administered

Intervention Name	mRNA-1345	Fluzone HD	Placebo
Concentration	CCI µg/vial	CCI mL/syringe	0.9% sodium chloride (normal saline)
Formulation	Suspension for Injection	Suspension for Injection	Sterile liquid for Injection
Route of Administration	IM	IM	IM

Abbreviations: HD = high dose; IM = intramuscular.

Study Intervention Packaging and Labeling

The study intervention used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH Guidance for Industry, GCP guidelines, guidelines for Quality System Regulations, and applicable regulations. The mRNA-1345 will be provided in vials, Fluzone HD in syringes. Each will be labeled as required per country requirement.

Study Arms and Dosing Regimens

The study arms and dosing regimens are listed in Table 4.

Table 4: Study Arms and Dosing Regimens

Arm Title	Arm 1	Arm 2
Arm Description	Day 1: Fluzone HD+mRNA-1345 CCI µg followed by Day 22: Placebo	Day 1: Fluzone HD+Placebo followed by Day 22: mRNA-1345 CCI µg

Abbreviation: HD = high dose.

6.2. Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator or authorized site staff are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Randomization will be stratified by age (65 to <75 years and ≥75 years [approximately 10%]).

Study intervention will be dispensed at the study visits as summarized in the SoA (Table 1).

Returned study intervention should not be redispensed to the participants.

6.4. Blinding

Refer to Section 9.1 for additional details on blinding.

As this is an observer-blind study, the Investigator, study clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention 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 study intervention for all participants. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded study clinic staff will administer the study intervention. 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 study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.

6.4.1. Unblinding

Investigators may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.5. Study Intervention Compliance

The study interventions will be administered at the study site under direct observation of medically qualified study staff, and study intervention administration will be appropriately recorded (date and time) in the eCRF. Qualified staff will confirm that the participant has received the entire dose of the study intervention. If a participant does not receive the study intervention, the reason for the missed dose will be recorded. Data will be reconciled with site accountability records to assess compliance.

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

6.6. Dose Modification

No dose modifications are allowed.

6.7. Continued Access to Study Intervention After the End of the Study

There will be no access to study intervention after EoS.

6.8. Treatment of Overdose

The mRNA-1345 will be provided in single dose vials, Fluzone HD in syringes, and are to be administered by a healthcare provider. It is unlikely that an overdose will occur. Should overdose occur, careful monitoring and follow-up must be performed.

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest (see below) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Specific categories of interest:

- All prior medications (including any prescription or OTC medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent.
- Any licensed seasonal influenza vaccine administered in the prior 12 months.
- Any licensed/authorized or investigational COVID-19 vaccine administered at any time before study intervention administration.
- Any vaccine (authorized or investigational) administered in the prior 12 months. For authorized influenza vaccines, detailed information regarding which vaccine was administered should be provided if available.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Prohibited Therapy

Participants must discontinue any of the medications listed in Section 5.2 for the specified period prior to baseline. These medications are prohibited for the duration of the study. Other medications being used at Screening may be continued.

6.9.2. Concomitant Medications, Therapies, and Procedures

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 for 21 days following each vaccination (Day 1 through Day 43). 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 Month 6 after the last study injection/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 each vaccination, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study clinic staff during the postinjection study site visits or via other participant interactions (eg, SCs).
- All concomitant procedures/surgeries at any time during the study period after study intervention dosing.

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, and the drug's pharmacology and pharmacokinetics. The Sponsor will decide 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.

6.9.3. 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 may not require withdrawal of the participant from the study but may determine a participant's evaluability in the PP analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study interventions 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 21 days after each study injection (until Day 43).

- Nonstudy influenza or RSV vaccine at any time during the study.
- Igs and/or any blood products administered during the study period.
- Medications that suppress the immune system.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.10.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study for follow-up and for any further evaluations that need to be completed (see the SoA [Table 1]).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an end of study call should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- A participant who withdraws from the study will not be replaced.
- 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.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit foreseen in the protocol. All data collected until the date of withdrawal or last contact of the participant will be used for the analysis. A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Information relative to the withdrawal will be documented in EDC. The Investigator will document whether the decision to withdraw a participant from the study was made by a

participant, or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study intervention
- Other
- Physician decision
- Protocol deviation
- Screen failure
- Study terminated by Sponsor
- Withdrawal by participant
- Withdrawal due to solicited ARs/reactogenicity

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study because of an SAE or AE until resolution of the event.

7.3. Lost to Follow-up

If a participant does not complete a visit within the time window specified in the SoA (Table 1), every effort should still be made to complete the assessments for that visit (even though outside of the defined visit window); the participant will continue with subsequent scheduled study visits per their original schedule (ie, relative to their Day 1 visit). If a participant still does not complete the visit after all these efforts, the visit will be classified as missed and all safety requirements of the missed visit will be captured and included in the subsequent visit.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits 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 lost to follow-up, 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 should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed.

7.4. Pause Rules

Not applicable.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- Study results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- If a visit cannot be scheduled within the indicated allowable window and/or the participant misses the visit, this is considered a protocol deviation. However, the visit should still be completed, if possible, to collect study data. Subsequent visits should be scheduled at the originally planned number of days after Day 1 defined in the SoA (Table 1).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations. Sample collection on Day 1 and Day 22 (ie, blood) must be performed prior to study intervention dosing.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

8.1. Demography

Demographic information relating to the participant's sex, age, and race will be recorded at Screening in EDC.

The medical history of each participant will be collected and recorded in EDC. Significant findings that were present prior to the signature of the informed consent will also be included in EDC.

8.2. 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 may be measured:

- RSV serum Abs, including nAbs and bAbs.
- Influenza virus serum Abs, measured by HAI assay.

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 10.1.3), 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 for additional assay development.

8.3. Safety Assessments

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

- Solicited local and systemic ARs that occur during the 7 days following each vaccine administration (ie, the day of study intervention dosing and 6 subsequent days [Days 1-7 and Days 22-28]). Solicited ARs will be recorded daily using eDiaries. Local solicited ARs will be recorded separately for each injection site. eDiary review by the site should occur daily on Day 1-Day 7 and Day 22-28. Additional review of the eDiary will occur at Day 8 and Day 29 between the site and the participant during the safety telephone calls.
- Unsolicited AEs observed or reported from the day of each injection and 20 subsequent days. Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- SAEs from the time of signing ICF through Month 6 (EoS) after the last study intervention dosing.
- AESIs, MAAEs, and AEs leading to discontinuation from study participation from vaccination on Day 1 through Month 6 after the last study intervention dosing (EoS) or withdrawal from the study.
- Vital sign measurements
- Physical examination findings
- Concomitant medications and nonstudy vaccinations

- Concomitant procedures

8.3.1. Physical Examinations

A complete physical examination, including height and weight, will be performed at the Screening Visit. A complete physical examination is not needed on Day 1 if Screening occurs within 7 days of Day 1.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- On the day of study intervention administration, before administration, the arms receiving the injection(s) should be examined and the associated lymph nodes should be evaluated.

Any clinically significant finding identified during the Screening Visit should be reported as medical history, and during study visits should be reported as a MAAE.

Symptom-directed physical examinations will be performed at other in-person visits, if clinically indicated (Table 1). Any clinically significant finding identified during a symptom-directed physical examination should be reported as an AE.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature will be measured at the time points indicated in the SoA (Table 1). The preferred route of temperature assessment is oral.

The participant will be seated for at least 5 minutes before all measurements are taken. On Day 1 and Day 22 vital sign measurements will be collected once before study intervention dosing and at least 30 minutes after study intervention dosing (before participants are discharged from the study site). If vital signs are clinically concerning, participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

Febrile participants on the study intervention dosing day (fever is defined as a body temperature ≥38.0°C/100.4°F) may be rescheduled within the relevant window periods. Criteria for delay of study intervention dosing are provided in Section 5.4.

An abnormal vital sign measurement should be assessed to determine if it meets AE reporting criteria per protocol and reported as an AE in the EDC, if appropriate. 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, is considered stable, or until the Investigator determines that follow-up is no longer medically necessary.

8.3.3. Use of Electronic Diaries

At the time of consent, the participants must confirm they are willing to complete an eDiary for 7-day reactogenicity after each vaccination. The local and systemic ARs that will be solicited by the eDiary are described in Table 7.

Solicited local and systemic reactogenicity ARs will be collected on the 7 days following each vaccine administration (ie, the day of study intervention dosing and 6 subsequent days [Days 1-7 and Days 22-28]). Details on the recording of solicited local and systemic ARs are included in Section 10.2.

At the dosing visit, participants will record data into the eDiary starting approximately 30 minutes after study intervention dosing under supervision of the clinic staff to ensure successful entry of assessments. The 30-minute observation period is an opportunity for clinic staff to train the participant on eDiary completion requirements. The clinic staff will perform any retraining as necessary.

At each dosing visit, participants will be instructed or reminded on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) side as the injection arm(s) during the 7 days after study injection(s). Daily oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the site staff.

The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1). If eDiary questions result in identification of relevant safety events according to the study period or symptoms, a follow-up safety call will be triggered (see Section 8.3.4). The information obtained during the safety call should be recorded in the appropriate source documentation.

If a participant does not respond to the eDiary questions according to the SoA, clinic staff will follow-up with the participant.

8.3.4. Safety Phone Calls

A safety phone call is a telephone call made to the participant by trained clinic staff. This call will follow a script, which will facilitate the collection of relevant safety information. Safety phone calls will follow a schedule for each participant, as shown in the SoA (Table 1). The participant will be interviewed according to the script about occurrence of unsolicited AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from study participation, concomitant medications associated with those events, and any nonstudy vaccinations. All safety information collected from the phone call must be documented in the source documents as described by the participant and not documented on the script used for the phone call. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event. A safety phone call may trigger an USV.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs, SAEs, solicited ARs, and unsolicited AEs can be found in Section 10.2.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the time of signing ICF through Month 6 after last study injection/EoS. AESI, MAAEs, and AEs leading to discontinuation from study participation will be collected from the start of study intervention dosing until Month 6 after each study injection (EoS) or withdrawal from the study, at the timepoints specified in the SoA (Table 1).

All solicited local and systemic ARs will be collected 7 days after study intervention dosing on Day 1 and Day 22 (ie, the day of study intervention dosing and 6 subsequent days).

All unsolicited AEs will be collected through the 21 days following each study intervention dosing (ie, the day of study intervention dosing and 20 subsequent days).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent (and that are not SAEs) will be recorded as medical history/current medical conditions, not as AEs; however, if the condition worsens at any time after study intervention administration, it will be recorded and reported as an AE.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

An eDiary has specifically been designed for this study by the Sponsor for collection of solicited ARs (see Section 8.3.3). At the time of consent, the participants must confirm they will be willing to complete the eDiary to record solicited ARs that occur during the 7 days following each vaccine administration (ie, the day of study intervention dosing and 6 subsequent days [Days 1-7 and Days 22-28]). The diary will include prelisted ARs (solicited ARs) and intensity scales.

At every in-person visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including surveillance for respiratory viral infection symptoms) for detection of unsolicited AEs, 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 OTC medications), or had any nonstudy vaccinations.

The Investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to the study intervention. 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 or AESI requiring immediate notification to the Sponsor or its designated representative.

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 10.2.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.

8.4.4. 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. For example, for reports that are required to be submitted to the European Union, individual case safety reports, will be submitted via the EudraVigilance Clinical Trial Module Gateway.

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/package insert and will notify the IRB, if appropriate according to local requirements.

For expedited reporting purposes, the expectedness of SAEs will be assessed against the investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB/package insert for investigational product(s) and comparator(s) will be considered unexpected.

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.

8.4.5. Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term “reactogenicity” refers to the occurrence of transient adverse effects associated with study intervention dosing. The eDiary will solicit daily participant reporting of ARs using a structured

checklist. Participants will record such occurrences in the eDiary on the day of each study intervention dosing and 6 subsequent days.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented Section 10.2, which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

If a participant reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study staff in EDC.

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 in EDC, where reactogenicity is collected.

If the participant reported an event that started after the solicited period (ie, beyond 7 days after dosing), it should be recorded as an AE in EDC. Causality for these events will be determined per assessment by the Investigator.

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 clinic staff in EDC, where reactogenicity is collected:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (MAAE).
- Solicited local or systemic AR lasting beyond 7 days poststudy intervention dosing.
- Solicited local or systemic AR that leads to participant discontinuation from study participation.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

8.4.6. Medically Attended Adverse Events

A MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (eg, emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured in EDC.

8.4.7. Adverse Events of Special Interest

The definition of AESI is provided in Section 10.2.4.

AESI for this protocol are listed in Section 10.3.

Investigators should report all events which fall into the categories as an AESI per the reporting processes specified in Section 10.2.6.

8.4.7.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention dosing should be recorded as AESIs and reported as an SAE (Section 10.2.6), based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitive 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
- Involving 2 or more organ systems, as follows:
  - Skin/mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes.
  - Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, 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, rhinorrhea.
  - Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting.

8.4.7.2. Myocarditis and/or Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (see Section 10.2.2).

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical trials per the CEAC charter, to determine if they meet CDC criteria for “probable” or “confirmed” events (Section 10.1.6.2).

The CDC Working Case Definitions are provided in Section 10.4 as guidance.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of the statistical analyses will be provided in the SAP, which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to 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.

9.1. Blinding and Responsibility for Analyses

An independent unblinded statistical and programming teams will perform the preplanned primary analysis (Section 9.6.1) and a final analysis. Prespecified Sponsor team members will be unblinded for these analyses and will not communicate the results to the blinded Investigators, study clinic staff, clinical monitors, or participants.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the study intervention in a secure location that is not accessible or visible to other study clinic staff. An opaque sleeve/blinding label over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1345, placebo, and Fluzone HD have a different appearance. Only delegated unblinded study clinic staff will conduct the injection procedure. Once the injections are completed, only the blinded study clinic staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

Procedures for breaking the blind in the case of a medical emergency are provided in Section 6.4.

9.2. Statistical Hypothesis

The immunogenicity primary objectives are to evaluate the effect of coadministered influenza vaccine with mRNA-1345 on the immune response to RSV-A and RSV-B virus and influenza A and B strains included in Fluzone HD. There are 6 coprimary endpoints to support the primary objectives.

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

Coprimary endpoints based on RSV-A GMT 21 days after mRNA-1345 administration:

The null hypothesis H^1_0: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by GMT at Day 22 (Arm 1) using RSV-A nAb assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by GMT at Day 43 (Arm 2) using RSV-A nAb assay. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD

compared with the GMT of RSV-A nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

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

Coprimary endpoints based on RSV-B GMT 21 days after mRNA-1345 administration:

The null hypothesis H^2_0: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD (Arm 1), as measured by GMT at Day 22 (Arm 1) using RSV-B nAb assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by GMT at Day 43 (Arm 2) using RSV-B nAb assay. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD compared with the GMT of RSV-B nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

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

Coprimary endpoints based on GMT 21 days after Fluzone HD administration:

The null hypotheses H^3_0 to H^6_0: immunogenicity response to Fluzone HD in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by GMT of influenza anti-HA Abs for each of the 4 influenza strains at Day 22 (both Arm 1 and Arm 2) using HAI assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD. For each of the 4 influenza strains, the noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD compared with the GMT of anti-HA Abs in participants who received mRNA-1345 sequentially with Fluzone HD.

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

Secondary endpoints based on SRR 21 days after mRNA-1345 administration:

The null hypothesis H^7_0: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SRR of RSV-A nAbs at Day 22 (Arm 1), is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by SRR of RSV-A nAbs at Day 43 (Arm 2). The noninferiority in the SRR in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD minus the SRR of RSV-A nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

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

Secondary endpoints based on SRR 21 days after mRNA-1345 administration:

The null hypothesis H^8_0: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SRR of RSV-B nAbs at Day 22 (Arm 1), is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by SRR of RSV-B nAbs at Day 43(Arm 2). The noninferiority in the SRR in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD minus the SRR of RSV-B nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

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

Secondary endpoint based on SCR 21 days after Fluzone HD administration:

The null hypotheses H^9_0 to H^{12}_0: immunogenicity response to Fluzone HD in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SCR of influenza anti-HA Abs for each influenza strain at Day 22 (for both Arm 1 and Arm 2) using HAI assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD. The noninferiority in SCR in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD 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 Fluzone HD minus the SCR of anti-HA Abs in participants who received mRNA-1345 sequentially with Fluzone HD.

9.3. Sample Size Determination

The study will plan to randomize approximately 1900 participants in a 1:1 ratio, with approximately 950 participants receiving Fluzone HD + mRNA-1345 followed by placebo (Arm 1) and 950 participants receiving Fluzone HD + placebo followed by mRNA-1345 (Arm 2).

With approximately 950 participants in each group, the study has approximately 95% probability to observe at least 1 participant with an AE at a true 0.3% AE rate in that group.

Assuming approximately 10% of participants are ineligible to be included in the PP Set, 855 participants will be included in each group. There is at least 98.5% power to demonstrate the noninferiority of the immune response to RSV-A and RSV-B, as measured by GMT of RSV-A and RSV-B nAb at Day 22 (Arm 1) or Day 43 (Arm 2) in participants receiving mRNA-1345 coadministered with Fluzone HD compared with that in mRNA-1345 sequentially administered with Fluzone HD, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 0.9. The standard deviation of the natural log-transformed level is assumed to be 1.5.

The global power considered adequate to meet the primary objectives and evaluate the immune responses to RSV-A, RSV-B, and influenza is at least 91.3%. Sample size justification for the coprimary endpoints is shown in Table 5.

Table 5: Sample Size Justification

Coprimary Endpoints	Number of Evaluable Participants (with 10% Ineligible for the PP Set)	α	Standard Deviation	GMR Assumption	NI Margin	Power
mRNA-1345 noninferiority (2-sided test)						
RSV-A GMT Day 22 (Arm 1) versus Day 43 (Arm 2)	855	0.05	1.5	GMR=0.9	1.5	98.5%
RSV-B GMT Day 22 (Arm 1) versus Day 43 (Arm 2)	855	0.05	1.5	GMR=0.9	1.5	98.5%
Fluzone HD noninferiority (2-sided test)						
GMT Day 22 (Arm 1) versus Day 22 (Arm 2)	855	0.05	1.5	GMR=0.9	1.5	98.5%
Overall power to show noninferiority on both mRNA-1345 and Fluzone HD						91.3%

Abbreviations: GMR = geometric mean titer ratio; GMT = geometric mean titer; HD = high dose; NI = noninferiority; PP = per protocol.

9.4. Analysis Sets

The analysis sets are described in Table 6:

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. Participants will be included in the treatment group to which they are randomized.
Full Analysis Set (FAS)	All randomized participants who received any study intervention. Participants will be included in the treatment group to which they are randomly assigned.
Per Protocol (PP) Set	Includes all participants in the FAS that received the assigned study intervention dose according to protocol, complied with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no major protocol deviations or conditions that impact the immune response. The PP Set will be the

Set	Description
	primary population used for the analysis of immunogenicity data. Participants will be included in the treatment group to which they are randomly assigned.
Solicited Safety Set	Includes all randomized participants who received any study intervention 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 treatment group corresponding to the study intervention they actually received.
Safety Set	Includes all randomized participants who receive any study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the Safety Set.

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

9.5. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the PP Set, unless otherwise specified. 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 coprimary endpoints include the GMT of RSV-A/RSV-B nAb titers at Day 22 (Arm 1) and Day 43 (Arm 2) and GMT of anti-HA Ab titers at Day 22 for each influenza strain. For each coprimary endpoint regarding GMT, the GMR will be estimated using an analysis of covariance model on the log-transformed titers, with the treatment group and 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 treatment groups. For each coprimary endpoint regarding GMT, the noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is >0.667.

The SRR of RSV-A/RSV-B nAbs is defined as proportion of participants with postvaccination titers ≥4×LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ. The SCR of an influenza strain is defined as proportion of participants with a postvaccination

titer ≥1:40 if baseline is <1:10 or a ≥4-fold rise in postvaccination HAI Ab titer if baseline is ≥1:10.

The number and percentage of participants with SRR at Day 22 (Arm 1) and Day 43 (Arm 2) or SCR at Day 22 will be provided with 2-sided 95% CI using the Clopper-Pearson method. For 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 corresponding timepoint between the treatment groups. For each strain, the noninferiority of SRR or SCR will be considered demonstrated if the LB of the 95% CI of the SRR or SCR difference is >-10% based on a noninferiority margin of 10%.

For the immunogenicity endpoints, the GMT/GMC ratio of specific Abs, with the corresponding 95% CI at each timepoint, and geometric mean fold rise (GMFR) of specific Ab titers, with the corresponding 95% CI at each postbaseline timepoint over preinjection baseline, will be provided by treatment 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 ULOQ will be converted to the ULOQ if actual values are not available.

The proportion of participants with at least 2-fold and SRR titers/concentration (relative to baseline) will be provided by timepoint with the 2-sided 95% CI using the Clopper-Pearson method as well.

Descriptive statistics (including 95% CIs) of the immunogenicity endpoints will also be provided by treatment group and age group (65 to 74 years, and ≥75 years).

9.5.2. Safety Analyses

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 treatment group, and by treatment cohort, as applicable, unless otherwise specified.

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

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

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

Solicited ARs will be coded according to the MedDRA for AR terminology. The toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.

Unsolicited AEs will be presented by MedDRA system organ class and preferred term. 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, AESIs, MAAEs, and AEs leading to discontinuation will be reported in summary tables accordingly. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

9.5.3. Exploratory Analyses (May Be Performed)

The GMC and GMFR of postinjection/baseline titers to RSV bAbs, the proportion of participants with ≥2-fold and 4-fold (SRR) increases in RSV bAb concentration will be summarized.

The frequency, specificities, or other endpoints to be determined for the further characterization of immune responses may also be explored. Exploratory analyses not addressed in this section will be described in the SAP before database lock.

9.6. Planned Analyses

9.6.1. Primary Analysis

The primary analysis of safety and immunogenicity will be performed after all participants have completed the Day 43 Visit. All data relevant to the primary study analysis through the Day 43 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. The SAP will describe the planned primary analyses in greater details.

9.6.2. Final Analysis

The final analysis of all endpoints will be performed after all participants have completed Day 202/EoS. Results of the analysis will be presented in a final CSR.

9.6.3. 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 and secondary endpoints.

The coprimary 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 coprimary endpoints need to be met successfully to declare the study a success to achieve noninferiority of coadministration.

The secondary endpoints on SRR and SCR will be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all coprimary endpoints have achieved statistical significance.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and Subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

The ICF will 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, influenza, and related viruses, including analyses related to the immunology of this vaccine, viral infection, and clinical conduct.

10.1.4. Recruitment Strategy

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

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

10.1.5. Data Protection

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

- The participant must be informed that their 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

10.1.6.1. Internal Safety Team

An IST will be formed to review primary and cumulative blinded and unblinded safety data on a regular basis.

10.1.6.2. Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review all reported cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (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 determine if additional action is needed. The CEAC operates under the rules of an approved charter. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review are defined in the charter.

10.1.7. Dissemination of Clinical Study Data

ModernaTX, Inc. shares information about clinical studies and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), etc., as well as some national registries.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 CRF.

- Guidance on completion of CRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the 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, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. 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.

10.1.9. Source Documents

- 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 CRF 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.
- Definition of what constitutes source data and its origin can be found in the source data declaration.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF 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.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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. 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.

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:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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.

10.1.11. 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.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include SAEs and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may 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 events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.2.3. Definition of MAAE

A MAAE is an AE that leads to an USV to a healthcare practitioner. This would include visits to a study site for unscheduled assessments not required per protocol (e.g., rash assessment, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (e.g., emergency room, urgent care, primary care physician).

10.2.4. Definition of AESI

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

The AESIs defined for this protocol can be found in Section 10.3.1.

10.2.5. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the eCRF /required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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. The intensity grading scale used in this study is presented in Table 7.

Table 7: Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	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 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	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	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	<38.0°C <100.4°F	38.0-38.4°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

Note: Events listed above but starting >7 days poststudy intervention dosing will be recorded in the eCRF. Causality for each event will be determined per assessment by the Investigator.

Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- Not related: There is not a reasonable possibility of a relationship to the study intervention. Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention.
- Related: There is a reasonable possibility of a relationship to the study intervention. There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.2.6. Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an EDC Tool

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the EDC tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor or Designee via Paper Data Collection Tool

- If EDC is unavailable and the site needs to use a paper form to report SAEs, email transmission of the SAE paper data collection tool may be used to transmit this information to the Sponsor.
- Initial notification via email does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.
- SAE reports should be emailed to PPD .

10.3. Appendix 3: Adverse Events of Special Interest

10.3.1. AESIs

Investigators should report all events that fall into the categories presented in Table 8 as an AESI per the reporting processes specified in Section 10.2. 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 8: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $<125\times10^9$ cells per liter. • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome.
New onset of or worsening of neurologic diseases	Neurologic diseases include the following: • Guillain-Barré Syndrome. • Acute disseminated encephalomyelitis.

Medical Concept	Additional Notes
	• 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 8.4.7.1. • Follow the reporting procedures in protocol Section 8.4.
Myocarditis/Pericarditis	• Myocarditis. • Pericarditis. • Myopericarditis.

Abbreviation: HELLP = hemolysis, elevated liver enzymes, and low platelet count.

10.4. Appendix 4: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 9 as guidance.

Table 9: Case Definitions of Probably and Confirmed Myocarditis, Pericarditis, and Myopericarditis 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:* • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.	Presence of ≥1 new or worsening of the following clinical symptoms:* • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.
	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.	**OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.

Condition	Definition	
	AND ≥1 new finding of • Troponin level above upper limit of normal (any type of troponin). • Abnormal ECG or EKG or rhythm monitoring findings consistent with myocarditis[§]. • Abnormal cardiac function or wall motion abnormalities on echocardiogram. • cMRI findings consistent with myocarditis[§§].	**AND** ≥1 new finding of • Histopathologic confirmation of myocarditis[†]. • cMRI findings consistent with myocarditis[§§] in the presence of troponin level above upper limit of normal (any type of troponin).
	AND • No other identifiable cause of the symptoms and findings.	**AND** • No other identifiable cause of the symptoms and findings.
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • Acute chest pain.[††] • Pericardial rub on exam. • New ST-elevation or PR-depression on EKG. • New or worsening pericardial effusion on echocardiogram or MRI.	
Myopericarditis	This term may be used for participants who meet criteria for both myocarditis and pericarditis.	

Abbreviations: cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

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

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

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

§§ Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon.

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

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

Reference: (Gargano et al 2021).

11. REFERENCES

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr., et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3-14.

Bartoszko J, Loeb M. The burden of influenza in older adults: Meeting the challenge. Aging Clin Exp Res. 2021;33(3):711-7.

Brighton Collaboration [homepage on the Internet]. The Task Force for Global Health. 2019 May 09. Safety Platform for Emergency Vaccines (SPEAC) [updated 2019 May 09; cited 2023 Jun 20]. Available from: https://brightoncollaboration.us/speac/.

ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US). Identifier NCT05330975. A Study of mRNA-1345 vaccine targeting respiratory syncytial virus (RSV) in adults ≥50 years of age (RSVictory). (2022 Nov 15; cited 2023 Jul 17). Retrieved from: https://clinicaltrials.gov/study/NCT05330975.

ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US). Identifier NCT05127434. A study to evaluate the safety and efficacy of mRNA-1345 vaccine targeting respiratory syncytial virus (RSV) in adults ≥60 tears of age. (2023 Dec 31; cited 2023 Jul 17). Retrieved from: https://clinicaltrials.gov/study/NCT05127434.

ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US). Identifier NCT05397223. A study of modified mRNA vaccines in healthy adults. (2024 Mar 25; cited 2023 Jul 17). Retrieved from: https://clinicaltrials.gov/study/NCT05397223.

ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US). Identifier NCT05585632. A safety, reactogenicity, and immunogenicity study of mRNA-1045 (influenza and respiratory syncytial virus [RSV]) or mRNA-1230 (influenza, RSV, and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) vaccine in adults 50 to 75 years old. (2024 Mar 15 (estimated); cited 2023 Jul 17). Retrieved from: https://clinicaltrials.gov/study/NCT05585632.

ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US). Identifier NCT04528719. A dose escalation study to evaluate safety, reactogenicity, and immunogenicity of mRNA-1345 in healthy adults and in children who are respiratory syncytial virus (RSV)-seropositive. (2023 Sep 30 (estimated); cited 2023 Jul 17). Retrieved from: https://clinicaltrials.gov/study/NCT04528719.

Crank MC, Ruckwardt TJ, Chen M, Morabito KM, Phung E, Costner PJ, et al; VRC 317 Study Team. A proof of concept for structure-based vaccine design targeting RSV in humans. Science. 2019;365(6452):505-9.

Czaja CA, Miller L, Alden N, Wald HL, Cummings CN, Rolfes MA, et al. Age-related differences in hospitalization rates, clinical presentation, and outcomes among older adults hospitalized with influenza-U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET). Open Forum Infect Dis. 2019;6(7):ofz225.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 2023 Jun 20]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352(17):1749-59.

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID 19 vaccine after reports of myocarditis among vaccine recipients: Update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-82.

GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: A systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017;17(11):1133-61.

Graham BS. Immunological goals for respiratory syncytial virus vaccine development. Curr Opin Immunol. 2019;59:57-64.

Kurzweil V, Tang R, Galinski M, Wang K, Zuo F, Cherukuri A, et al. Translational sciences approach to RSV vaccine development. Expert Rev Vaccines. 2013;12(9):1047-60.

Looney RJ, Falsey AR, Walsh E, Campbell D. Effect of aging on cytokine production in response to respiratory syncytial virus infection. J Infect Dis. 2002;185(5):682-5.

McLellan JS, Chen M, Joyce MG, Sastry M, Stewart-Jones GB, Yang Y, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. Science. 2013;342(6158):592-8.

Monto AS. Reflections on the global influenza surveillance and response system (GISRS) at 65 years: An expanding framework for influenza detection, prevention, and control. Influenza Other Respir Viruses. 2018;12(1):10-2.

Ngwuta JO, Chen M, Modjarrad K, Joyce MG, Kanekiyo M, Kumar A, et al. Prefusion F-specific antibodies determine the magnitude of RSV neutralizing activity in human sera. Sci Transl Med. 2015;7(309):309ra162.

Riedel S, Hobden JA, Miller S, Morse SA, Mietzner TA, Detrick B, et al. Orthomyxoviruses (Influenza Viruses). In: Jawetz, Melnick & Adelberg's Medical Microbiology. 28th ed. New York: McGraw-Hill Education; 2019. p. 581-94.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

Sanofi Pasteur. Fluzone HD Quadrivalent [package insert]. U.S. Food and Drug Administration website https://www.fda.gov/media/139731/download. Revised January 2023. Accessed 13 Jul 2023.

Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: A systematic review and meta-analysis. J Infect Dis. 2020;222(Suppl 7):S577-83.

Walsh EE, Peterson DR, Kalkanoglu AE, Lee FEH, Falsey AR. Viral shedding and immune responses to respiratory syncytial virus infection in older adults. J Infect Dis. 2013;207(9):1424-32.

World Health Organization (WHO) [homepage on the Internet]. Influenza (seasonal): Ask the expert: influenza Q&A. [updated 12 January 2023; cited 2023 Jun 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations-a post-marketing surveillance review. Eur J Pediatr. 2002;161(1):21-5.

Signature Page for VV-CLIN-011142 v1.0

2nd Approval	PPD (Moderna) 21-Jul-2023 13:11:01 GMT+0000

Signature Page for VV-CLIN-011142 v1.0