CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age	
Protocol Number:	mRNA-1345-P301	
Amendment Number:	3	
Amendment Scope	Global	
Study Phase	2/3	
Sponsor Name	ModernaTX, Inc.	
Legal Registered Address:	200 Technology Square Cambridge, MA 02139	
Regulatory Agency Identifier Number(s):	**Registry**	**ID**
	Investigational New Drug Number:	23342
	EudraCT Number:	2021-005026-20
	IRAS ID:	1004704
Date:	30 Oct 2023	

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

CONFIDENTIAL

This document contains confidential information, which should not be copied, referred to, released to, or published by anyone without written approval from ModernaTX, Inc.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age" dated 30 Oct 2023 and the most recent version of the Investigator's Brochure.

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) Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance,* and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without Institutional Review Board (IRB)/Independent Ethics Committee (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 sub-investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient, study 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, US federal regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	**Date**

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	30 Oct 2023
Amendment 2	16 Nov 2022
Amendment 1	22 Sep 2022
Original Protocol	07 Oct 2021

Amendment 3 (30 Oct 2023)

This amendment is considered to be nonsubstantial because it neither impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the amendment is 1) to add unblinding of all participants at or shortly after Month 24 to inform participant's decision-making regarding receipt of a commercially available RSV vaccine and 2) to incorporate changes from a US-specific amendment that added a substudy (Part B, to be conducted at select US sites) to evaluate the safety, tolerability, and immunogenicity of revaccination with a 50-µg booster dose of mRNA-1345 given approximately 24 months after a primary dose of mRNA-1345 (administered in Part A) in adults ≥ 60 years of age.

The summary of changes table describes the changes made in Amendment 3 relative to Amendment 2, including the sections modified and the corresponding rationales. The protocol was restructured in Amendment 3. Section numbers in the summary of changes table reflect the updated section numbers. The List of Abbreviations and References were updated, as needed. Other minor editorial or formatting changes are not included in the summary of changes table.

Summary of Major Changes in Protocol Amendment 3

Section # and Name	Description of Change	Brief Rationale
Title Page and Protocol Approval – Sponsor Signatory Page	Updated medical monitor/sponsor signatory name and contact information.	Change in medical monitor/sponsor signatory.
1.1 Synopsis	Added Part B content. Labeled Part A content as such. Revised duration of Part A to account for possible early conduct of the Month 24 visit for Part B screening.	To add US-specific booster substudy (Part B).
1.2 Schema	Added study schema for Part B.	To add US-specific booster substudy (Part B).
2.2 Background and Overview; 2.2.2 Clinical Studies	Updated section.	To include current epidemiological and clinical data.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Potential Benefits of Study Participation	Revised for Part B and to account for VE results from Part A.	To add US-specific booster substudy (Part B).
2.3.2 Risks from Study Participation and Their Mitigation	Updated with the Sponsor's current position on myo- and pericarditis.	To ensure participant safety.
2.3.3 Overall Benefit/Risk Conclusion	Revised for Part B.	To add US-specific booster substudy (Part B).
3 Part A (including all subsections)	Added "Part A" to all headings and table and figure titles.	To distinguish Part A from Part B.
3.2.1 General Design (Part A)	Revised duration to account for possible early conduct of the Month 24 visit for Part B screening.	To add US-specific booster substudy (Part B).
3.4.2.8.1 Planned Unblinding (Part A)	Added by-participant unblinding at or shortly after the Month 24 visit for all participants.	To inform participant's decision-making regarding receipt of a commercially available RSV vaccine.
3.4.2.8.1 Planned Unblinding (Part A)	Added planned unblinding of participants after consenting to Part B participation and meeting initial eligibility criteria. Specified that participants who do not meet eligibility criteria will complete study activities in Part A according to the Part A SoE.	To add US-specific booster substudy (Part B).
3.4.4.2 Concomitant Medications and Therapies (Part A)	Clarified that, in addition to concomitant medications, any nonstudy vaccinations used to prevent COVID-19, RSV disease, or any other infectious disease will be collected.	To ensure there is documentation of receipt of RSV vaccines, which were not available when the protocol was last amended.
3.6 Study Assessments and Procedures (Part A)	Added that for the subset of participants at select US sites who consent to participation in the Part B substudy, conduct of the Month 24 visit up to 3 months (90 days) early is not a protocol deviation. Specified that participants who do not meet eligibility criteria will complete study activities in Part A according to the Part A SoE.	To add US-specific booster substudy (Part B).
3.6.1.3 Surveillance for RSV-Like Illness	Added adenovirus to list of pathogens for detection via nasopharyngeal swab.	To correct typographical error.
3.6.4.3 Independent Cardiac Event Adjudication Committee (Part A)	Updated with the Sponsor's current position on myo- and pericarditis.	To ensure participant safety.

Section # and Name	Description of Change	Brief Rationale
4 Part B Substudy (Select US Sites Only)	Added a Phase 3 randomized, observer-blinded, placebo-controlled substudy of a BD of 50 µg mRNA-1345 administered approximately 24 months after a primary dose of mRNA-1345. Part B will be conducted at select US sites only.	To evaluate the safety, tolerability, and immunogenicity of a BD of 50 µg of mRNA-1345 administered approximately 24 months after the primary dose.
6.1 Schedule of Events Table 20: Schedule of Events (Part A Phase 2 Segment); Table 21: Schedule of Events (Part A Phase 3 Segment)	Added to Footnote #1 that for the subset of participants at select US sites who consent to participation in the Part B substudy, conduct of the Month 24 visit up to 3 months (90 days) early is not a protocol deviation.	To add US-specific booster substudy (Part B).
6.1 Schedule of Events Table 22: Schedule of Events (Part B Substudy) (Select US Sites Only)	Added SoE for Part B.	To add US-specific booster substudy (Part B).
6.2.2 Study Monitoring	Clarified that the DSMB is only for Part A.	To add US-specific booster substudy (Part B).
6.5 Appendix 5: SAE Contact Information for Reporting	Removed fax number.	To provide current communication methods.

Abbreviations: BD = booster dose; COVID-19 = coronavirus disease 2019; DSMB = drug and safety monitoring board; RSV = respiratory syncytial virus; SOE = Schedule of Events; VE = vaccine efficacy.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Number: **mRNA-1345-P301**

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age

Study Phase: 2/3

Objectives and Endpoints for Part A:

The primary objectives and endpoints for Part A are below.

Primary Objectives	Primary Endpoints
Safety Objective	**Safety Endpoints**
• To evaluate the safety and tolerability of the mRNA-1345 vaccine.	• Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) up to 7 days post-injection. • Unsolicited adverse events (AEs) up to 28 days post-injection. • Medically-attended adverse events (MAAEs), adverse events of special interest (AESIs), serious adverse events (SAEs), and AEs leading to withdrawal up to 24 months post-injection.
Efficacy Objective	**Efficacy Endpoints**
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-associated lower respiratory tract disease (RSV-LRTD) as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection. • Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically-attended adverse event; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SAE = serious adverse event.

The key secondary efficacy objectives and endpoints for Part A are below.

Key Secondary Efficacy Objectives	Key Secondary Efficacy Endpoints
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-associated	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-ARD within the period of

acute respiratory disease (RSV-ARD) as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	14 days post-injection up to 12 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

Abbreviations: RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease.

The other secondary efficacy objectives and endpoints for Part A are below.

Secondary Objectives	Secondary Endpoints
Efficacy Objectives	**Efficacy Endpoints**
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause hospitalizations as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent all-cause LRTD within the period of 14 days post-injection up to 12 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection. • Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection.

• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo by RSV subtype.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD by RSV subtype A and RSV subtype B.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine on the change from baseline in frailty status at 12 months and 24 months.	• Change in total frailty score from baseline to 12 months and 24 months post-injection, using the EFS.
Immunogenicity Objective	**Immunogenicity Endpoints**
• To evaluate the Ab response to a single dose of mRNA-1345 vaccine from baseline up to 24 months post-injection.	• GMT of serum RSV neutralizing Abs and GMC of serum RSV binding Abs at prespecified study timepoints from baseline up to 24 months post-injection. • SRR in RSV neutralizing Abs up to 24 months post-injection. • GMFR from baseline at prespecified study timepoints up to 24 months post-injection. • Proportion of participants with ≥ 2-fold increase in Ab titer from baseline at prespecified study timepoints up to 24 months post-injection.

Abbreviations: Ab = antibody; EFS = Edmonton Frail Scale; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SRR = seroresponse rate.

The exploratory objectives for Part A are as follows:

- To evaluate immune response biomarkers after dosing with mRNA-1345 vaccine as potential correlates of protection or risk of RSV disease.
- To conduct additional analyses relating to further understanding of infection and disease associated with RSV and related pathogens, including analyses

related to the immunology of vaccination, viral infection, and clinical conduct.

- To describe the effect of immunization with mRNA-1345 vaccine on the prevention or mitigation of RSV-LRTD and all-cause LRTD with at least 1, 2, 3, 4, or 5 symptoms or signs of lower respiratory tract involvement.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause hospitalizations as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause ARD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-ARD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause ARD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on level of care required for daily living.
- To evaluate the effect of a single dose of mRNA-1345 vaccine on prevention of exacerbations of congestive heart failure (CHF) up to 12 months and 24 months post-injection.
- To evaluate the effect of a single dose of mRNA-1345 vaccine on prevention of exacerbations of chronic obstructive pulmonary disease (COPD) up to 12 months and 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-LRTD by baseline frailty status.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-ARD by baseline frailty status.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-LRTD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease, if feasible and relevant.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-ARD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease, if feasible and relevant.
- To describe the effect of a single dose of mRNA-1345 vaccine on death from all causes at 12 months and 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on the

change from baseline in health-related quality of life (HRQoL) at 12 months and 24 months using the 5-level EuroQol 5 Dimension (EQ-5D-5L) utility index scores.

- To describe the effect of a single dose of mRNA-1345 vaccine on HRQoL for participants with RSV-LRTD or RSV-ARD using the EQ-5D-5L utility index scores.
- To describe the effect of a single dose of mRNA-1345 vaccine on Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI) impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with RSV-LRTD or RSV-ARD.
- To describe the effect of a single dose of mRNA-1345 vaccine on the prevention or mitigation of the following:
  - Healthcare encounters (medical attendance and hospitalizations) associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD.
  - Duration of hospital encounters associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD.
  - Prescriptions for medications including antibiotics associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD.
- To explore the feasibility of linking patient-level data to real-world electronic health databases to extend the duration of monitoring for healthcare utilization or encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes (US sites only).

Economic Analysis for Part A

A separate economic analysis is planned to estimate the impact of vaccination with mRNA-1345 on QoL-adjusted survival and on healthcare costs in real-world practice in one or more geographies. If performed, this analysis would use information on clinical, QoL, and resource use outcomes collected within the study to estimate QoL and costs to a healthcare payer comparing a strategy of vaccination with mRNA-1345 to no vaccination. This analysis would be conducted under a separate analysis plan and be intended for submission to health technology assessment and payer audiences to support use of mRNA-1345 following launch.

Linkage to Real-World Data for Part A

To further extend the duration of monitoring for medical product utilization or healthcare encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes, a subset of consenting participants at US sites may be enrolled into substudies or subanalyses that allow linkage or tokenization to these systems.

Objectives and Endpoints for Part B Substudy (Select US Sites Only):

The primary objectives and endpoints for the Part B substudy are below.

Primary Safety Objectives	Primary Safety Endpoints
• To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose.	• Numbers and percentages of participants with: – Solicited local and systemic ARs through 7 days post-BD injection. – Unsolicited AEs through 28 days post-BD injection. – MAAEs, AESIs, SAEs, and AEs leading to withdrawal through BD Day 181/EOS.
Coprimary Immunogenicity Objectives	**Coprimary Immunogenicity Endpoints**
• To demonstrate noninferiority of the serum RSV-A nAb response of a BD of mRNA-1345 compared with a primary dose.	• GMT of serum RSV-A nAb at BD Day 29. • GMR of serum RSV-A nAb GMT at BD Day 29 over serum RSV-A nAb GMT at Primary Dose Day 29.
• To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.	• GMT of serum RSV-B nAb at BD Day 29. • GMR of serum RSV-B nAb GMT at BD Day 29 over serum RSV-B nAb GMT at Primary Dose Day 29.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BD = booster dose; EOS = end of study; GMR = geometric mean ratio; GMT = geometric mean titer; MAAE = medically-attended adverse event; nAb = neutralizing antibody; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SAE = serious adverse event.

The secondary objectives and endpoints for the Part B substudy are below.

Secondary Immunogenicity Objectives	Secondary Immunogenicity Endpoints
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 administered 24 months after the primary dose of mRNA-1345 based on seroresponse.	• SRR difference between serum RSV-A nAb at BD Day 29 and serum RSV-A nAb at Primary Dose Day 29. • SRR difference between serum RSV-B nAb at BD Day 29 and serum RSV-B nAb at Primary Dose Day 29.
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 up to	• GMT of serum RSV-A nAb at BD Day 1 and BD Day 181/EOS.

6 months post-BD injection.	• GMFR of serum RSV-A nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • GMT of serum RSV-B nAb at BD Day 1 and BD Day 181/EOS. • GMFR of serum RSV-B nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • SRR of serum RSV-A nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • SRR of serum RSV-B nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS.

Abbreviations: BD = booster dose; EOS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; nAb = neutralizing antibody; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate.

The exploratory objectives and endpoints for the Part B substudy are below.

Exploratory Immunogenicity Objectives	Exploratory Immunogenicity Endpoints
• To evaluate the long-term immune response to RSV-A and RSV-B among Part B participants who received placebo.	• GMT of serum RSV-A nAb and RSV-B nAb at prespecified study timepoints. • GMFR of serum RSV-A and RSV-B relative to pre-Primary Dose (baseline) at prespecified study timepoints. • SRR of serum RSV-A nAb at prespecified study timepoints. • SRR of serum RSV-B nAb at prespecified study timepoints. • Proportion of participants with ≥ 2-fold increase in serum RSV-A and RSV-B nAb levels from pre-Primary Dose (baseline) at prespecified study timepoints.
• To evaluate occurrence of RSV disease after a BD of mRNA-1345.	• Number and incidence of cases of the following: • RSV-LRTD with 2 or more symptoms

	• RSV-LRTD with 3 or more symptoms • RSV-ARD • Hospitalization From 14 days post-BD injection to BD Day 181/EOS

Abbreviations: BD = booster dose; EOS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; nAb = neutralizing antibody; RSV = respiratory syncytial virus; RSV-A = respiratory syncytial virus-A; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-B = respiratory syncytial virus-B; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SRR = seroresponse rate.

Study Design and Methodology of Part A:

This is a Phase 2/3, randomized, observer-blind, placebo-controlled, case-driven study to evaluate the safety and efficacy of mRNA-1345 vaccine as compared with placebo in adults ≥ 60 years of age. Immunogenicity of mRNA-1345 vaccine will be characterized and investigation for correlates of risk will be undertaken. The study will be conducted in 2 phases: Phase 2 and Phase 3 under the oversight of an independent DSMB.

Each phase of the study will have a screening period (up to 14 days before study injection), a single dose of study injection (Day 1), and a follow-up period (up to 24 months after study injection). The study duration will be approximately 25 months for each participant, except for a subset of participants at select US sites who may complete the Day 730 (Month 24) visit up to 3 months (90 days) early to allow screening activities for the Part B substudy. All participants will complete up to 8 scheduled visits at the clinic or mobile site, including Screening, Day 1, Day 15 (for Phase 2), Day 29, Day 181, Day 365, Day 546, and Day 730. All participants will have a safety contact (via telephone, email, text message, or other electronic means) on Day 8, Day 15 (for Phase 3), Day 60, and then monthly (ie, every 30 days).

Each participant will receive a single dose of study injection (50 µg mRNA-1345 or placebo) as a 0.5-mL intramuscular (IM) injection on Day 1.

Participants will be given and trained to use an electronic diary (eDiary) on the day of study injection (Day 1) to report solicited ARs and all other AEs for 7 days after the study injection.

Active and passive surveillance will be conducted for RSV-like illness and exposure to individuals with known RSV, also using the eDiary, starting from Day 15 (14 days after the study injection) until Day 730. If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant. The unscheduled visit will be performed within 5 days, if possible, after symptom onset or worsening, for medical evaluation and nasopharyngeal swab collection. All efforts must be made to collect a nasopharyngeal swab within 5 days of symptom onset for medical evaluation; however, if 5 days have elapsed since first symptom onset, swabs should still be collected as soon as possible, and this is not considered a protocol deviation. If a participant reports RSV-like symptoms prior to the active and passive surveillance period (which starts on Day 15), the site staff should still arrange an illness visit; this is not considered a protocol deviation. All participants who report symptoms of RSV-like illness will receive eDiary prompts to complete the patient-reported outcomes (PRO) questionnaires.

Safety contacts and eDiary safety prompts will be performed throughout the study and are intended to capture SAEs, MAAEs, hospitalizations, and outpatient treatments related to or for the treatment of the MAAEs or SAEs, AESIs, AEs leading to withdrawal, concomitant medications associated with these events, and/or receipt of nonstudy vaccinations. If an eDiary prompt results in the identification of a relevant safety event, a follow-up safety contact will be triggered, and an unscheduled visit may be performed.

All participants will be assessed for safety, efficacy, and immunogenicity endpoints up to 24 months after the study injection.

Participants will be considered to have completed the study if they complete the final visit at Day 730 (Month 24), 24 months following the receipt of study injection. The end of study (EOS) is defined as completion of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study globally.

Except for appropriately delegated unblinded pharmacists, vaccine administrators, clinical study managers, and monitors, all personnel involved in the conduct of the study will remain blinded to individual vaccination assignment until planned study unblinding.

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

The study design elements specific to the Phase 2 and Phase 3 segments of the study are explained below.

Phase 2 Segment

In the Phase 2 segment (US sites only), approximately 2000 participants will be randomly assigned to receive a single injection of 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Assignment will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent).

There will be safety data reviews at predefined intervals throughout the study. The safety reviews will be performed by both a blinded Internal Safety Team (IST) and an independent unblinded DSMB according to a specified monitoring plan outlined in a charter. The IST will comprise members not directly involved in the study. The DSMB will be composed of external independent subject matter experts and an unblinded statistician. The IST will conduct ongoing blinded safety reviews throughout the conduct of the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB will conduct unblinded reviews of safety data on a periodic basis as defined in a DSMB charter or as otherwise requested by the study team.

Final sample size of the Phase 2 segment will depend on real-time local surveillance of RSV circulation. The DSMB will review the Day 29 safety data from the first 400 participants who receive the study injection while further enrollment in the Phase 2 segment remains ongoing based on RSV surveillance information. Enrollment in the Phase 2 segment may expand up to 2000 participants if RSV surveillance data that are external to this study demonstrate a rise in RSV cases in a given region. No more than 2000 participants will be enrolled while the DSMB is reviewing the safety data from the Phase 2 segment of the study.

Participants in the Phase 2 segment will contribute to the planned Phase 3 analyses in a continuous Phase 2/3 study design.

Phase 3 Segment

Enrollment in Phase 3 segment of the study will be triggered by the DSMB review of the Day 29 safety data from the first 400 participants in the Phase 2 segment of the study. In the Phase 3 segment, approximately 35,000 participants will be randomly assigned to receive a single injection of either 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Assignment will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent).

This is a case-driven study and thus final sample size of the Phase 3 segment will depend on real-time local surveillance of RSV circulation external to the study and the sample size of the Phase 2 segment. The total study sample size including the participants in Phase 2 and Phase 3 segments of the study will be approximately 37,000.

If the prespecified criteria for early efficacy are met at the time of any interim analysis (IA) or overall efficacy at the primary analysis, a final study report describing the safety and efficacy of mRNA-1345 will be prepared based on the data available at that time. In the event that success criteria are met either at the time of the IA or when the total number of cases toward the primary endpoint have accrued, participants will continue to be followed in a blinded fashion until Month 24 to enable assessment of long-term VE.

Participants in both the Phase 2 and the Phase 3 segments will contribute to the planned safety, efficacy, and immunogenicity analyses.

Study Design and Methodology of Part B Substudy (Select US Sites Only):

Part B is a Phase 3, randomized, observer-blinded, placebo-controlled substudy to evaluate the safety, tolerability, and immunogenicity of revaccination with a BD of 50 µg of mRNA-1345 in participants who were randomized to and were subsequently vaccinated with the mRNA-1345 study injection in Part A. For the purposes of this substudy, the terms revaccination and booster are used interchangeably. The Part B substudy will be conducted at select US sites only.

Approximately 1500 participants will be randomly assigned in a 2:1 randomization ratio to receive a single BD injection of either 50 µg mRNA-1345 or placebo.

Participants will be consented and screened for Part B at the Month 24/EOS visit for Part A, which may be conducted up to 3 months (90 days) early. Potential participants must sign the consent to Part B ICF and undergo screening activities to confirm initial eligibility (ie, the participant meets all inclusion and exclusion criteria aside from Inclusion Criterion #5 [randomized to and subsequently received mRNA-1345 in Part A]). For participants who meet initial eligibility, vaccination group assignment will be unblinded to designated unblinded site staff. Participants who meet all eligibility criteria, including Inclusion Criterion #5, are eligible for the Part B substudy. Participants who are not eligible for Part B will complete study activities in Part A according to the Part A SoE.

Part B study duration will be approximately 6 months for each participant. All participants will complete up to 4 scheduled in-person visits, including Screening/BD Day 1, BD Day 29, and BD Day 181/EOS. All participants will have a safety contact (via telephone, email, text message, or other electronic means) on BD Day 8, BD Day 60, and every 60 days thereafter.

	Participants will be given and trained to use an eDiary on the day of study injection (BD Day 1) to report solicited ARs and all other AEs for 7 days after the study injection. Safety contacts will be performed throughout the substudy and are intended to capture SAEs, MAAEs, hospitalizations, and outpatient treatments related to or for the treatment of the MAAEs or SAEs, AESIs, AEs leading to withdrawal, concomitant medications associated with these events, and/or receipt of nonstudy vaccinations. All participants will be assessed for immunogenicity endpoints at BD Day 1, BD Day 29, and BD Day 181/EOS. Active and passive surveillance will be conducted for RSV-like illness and exposure to individuals with known RSV, also using the eDiary, starting 14 days after the study injection until BD Day 181/EOS. If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant. The unscheduled visit will be performed within 5 days, if possible, after symptom onset or worsening, for medical evaluation and nasopharyngeal swab collection. All participants will be assessed for safety, immunogenicity, and RSV surveillance/infection endpoints up to 6 months after the BD study injection. Participants will be considered to have completed the substudy if they complete the final visit at BD Day 181, 6 months after receiving the BD study injection. The EOS for Part B is defined as completion of the last visit of the last participant in the substudy or last scheduled procedure for the last participant in the substudy. Except for appropriately delegated unblinded pharmacists, vaccine administrators, clinical study managers, and monitors, all personnel involved in the conduct of the substudy will remain blinded to individual vaccination assignment until planned study unblinding. Safety will be closely monitored and reviewed by the ongoing IST. This substudy will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.
Randomization for Parts A and B:	In the Phase 2 segment of Part A, approximately 2000 participants will be randomly assigned to receive a single injection of either 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. In the Phase 3 segment of Part A, approximately 35,000 participants will be randomly assigned to receive a single injection of either 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. In Part B, approximately 1500 participants at select US sites will be randomly assigned to receive a single BD injection of either 50 µg of mRNA-1345 or placebo in a 2:1 randomization ratio. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pregenerated randomization schedules. Only the unblinded personnel will have controlled access to which vaccination group the participant is randomly assigned.
Stratification for Part A:	In both Phase 2 and Phase 3 segments of Part A of the study, assignment to vaccination groups will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent). The study will target enrollment of approximately 30% of participants 70 to 79 years of age, and

approximately 10% of participants ≥ 80 years of age. Risk will be defined based on the study participant's relevant past and current medical history. Participants will be categorized as at risk for LRTD if they have at least one of the following risk factors at Screening:

- CHF
- COPD

Randomization will not be stratified for the Part B substudy.

Study Population for Part A:

Inclusion Criteria

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

1. Adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses (including CHF [including heart failure with preserved ejection fraction] and COPD) but should be medically stable as assessed by the following criteria:
   - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity.
   - Absence of medical events qualifying as SAEs within 1 month of the planned study injection on Day 1.
   - Absence of known, current, and life-limiting diagnoses, which could continue for the duration of the primary efficacy period (12 months from study injection on Day 1) and which, in the opinion of the investigator, would make completion of the protocol unlikely.
2. Body mass index from ≥ 18 kg/m^2 to ≤ 35 kg/m^2.
3. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
4. Able to comply with study requirements.

Exclusion Criteria

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

1. Participation in another clinical research study where participant has received an investigational product (drug/biologic/device with the exception of investigational RSV products) within 6 months before the planned date of the Day 1 study injection. Current participation in another RSV investigational study is exclusionary.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
3. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease.
   Note: Human immunodeficiency virus (HIV) positive participants with CD4 count ≥ 350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50-500 viral copies which do

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

Note: To clarify, participants with stable autoimmune diseases that do not require systemic immunosuppressants (per Exclusion Criterion #9) are permitted.

4. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or any components of the mRNA-1345 vaccine.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
8. Received or plans to receive any nonstudy vaccine (including authorized or approved vaccines for the prevention of coronavirus disease 2019 [COVID-19] regardless of type of vaccine) within 28 days before or after the Day 1 study injection. Nonstudy vaccination(s) should not be delayed.
9. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
10. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study injection or during the study.
11. Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥ 37.8°C (100.0°F) on the planned day of vaccine administration).
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. Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure > 160 mmHg at the Screening or baseline (Day 1) visit.
14. Known history of hypotension, or systolic blood pressure < 85 mmHg at the Screening or baseline (Day 1) visit.
15. Diastolic blood pressure > 90 mmHg at the Screening or baseline (Day 1) visit.
16. Known uncontrolled disorder of coagulation.
    Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease

or stroke in the setting of atrial fibrillation and under good control will NOT be excluded.

17. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
18. Donated ≥ 450 mL of blood products < 14 days prior to Screening.
19. Member of study personnel or is an immediate family member or household member of study personnel.

Study Population for Part B Substudy (Select US Sites Only):

Inclusion Criteria

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

1. Adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses (including CHF [including heart failure with preserved ejection fraction] and COPD) but should be medically stable as assessed by the following criteria:
   - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity.
   - Absence of medical events qualifying as SAEs within 1 month of the planned study injection on BD Day 1.
   - Absence of known, current, and life-limiting diagnoses, which could continue for the 6 months from study injection on BD Day 1, and which, in the opinion of the investigator, would make completion of the protocol unlikely.
2. Body mass index from ≥ 18 kg/m^2 to ≤ 35 kg/m^2.
3. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
4. Able to comply with study requirements.
5. Randomized to and were subsequently vaccinated with the mRNA-1345 study injection in Part A at least 21 months prior to Screening.

Exclusion Criteria

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

1. Participation in another clinical research study where participant has received an investigational product (drug/biologic/device) within 6 months before the planned date of the BD study injection (BD Day 1). Current participation in another RSV investigational study is exclusionary.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

3. Certain immune-mediated conditions that are stable and well-controlled (eg, Hashimoto thyroiditis), as well as those that do not require systemic immunosuppressants per Exclusion Criterion #10 (eg, asthma, psoriasis, or vitiligo) may be permitted at the discretion of the investigator.

   Note: HIV positive participants with CD4 count ≥ 350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy) as determined from participant's medical records, are permitted.

   Note: To clarify, participants with stable autoimmune diseases that do not require systemic immunosuppressants (per Exclusion Criterion #10) are permitted.
4. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or any components of the mRNA-1345 vaccine.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
8. Received or plans to receive any nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 14 days before or after the BD Day 1 study injection. Nonstudy vaccination(s) should not be delayed.

   Note: Commercial influenza vaccine may be given at any time, but ideally at least 7 before or after the BD study injection. If participant receives an influenza vaccine, this should be captured within the concomitant medication eCRF.
9. Received or plans to receive any commercial RSV vaccination at any time prior to BD study injection (BD Day 1) or during the substudy.
10. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the BD study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
11. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the BD study injection or during the substudy.
12. Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥ 37.8°C [100.0°F] on the planned day of BD study injection).
13. 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 substudy or could interfere with the interpretation of study results.

14. Known uncontrolled disorder of coagulation.
    Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation and under good control will NOT be excluded.
15. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
16. Donated ≥ 450 mL of blood products < 14 days prior to Screening.
17. Member of study personnel or is an immediate family member or household member of study personnel.

Efficacy Assessments for Parts A and B:

Efficacy assessments related to RSV infection are defined below (Parts A and B).

Endpoint	Definition
RSV-LRTD with 2 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 2 or more of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.
RSV-LRTD with 3 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 3 or more of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.
RSV-ARD	RT-PCR-confirmed RSV infection **PLUS** an acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths

	per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-ARD.

Other efficacy assessments are defined below (Part A).

Endpoint	**Definition**
All-cause LRTD	New or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause LRTD.
All-cause ARD	An acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause ARD.

Surveillance for RSV-Like Illness

Starting from 14 days after the study injection and until EOS, participants will enter an active and passive surveillance period for respiratory disease. Surveillance will include the following:

- Provision of a Participant ID Card, which provides details on study participation, site contact information, and a list of symptoms of respiratory disease. Participants should present this card when they visit

healthcare providers not affiliated with the study who encounter participants with symptoms of respiratory disease.

- Part A: The eDiary will provide weekly prompts (every 7 days) to elicit symptoms of RSV-like illness (new onset or worsening) and exposure to individuals with known RSV.
- Part B: The eDiary will provide monthly prompts (every 30 days) to elicit symptoms of RSV-like illness (new onset or worsening) and exposure to individuals with known RSV.
- Participants will be contacted by the study staff if they have missed reporting in the eDiary.
- Part A: If symptoms arise or worsen after the participant has completed the eDiary entry for a given week, the participant should contact the site to report symptoms of RSV-like illness.
- Part B: If symptoms arise or worsen after the participant has completed the eDiary entry for a given month, the participant should contact the site staff to report symptoms of RSV-like illness.
- If a participant reports RSV-like symptoms prior to the active and passive surveillance period (which starts 14 days after study injection), the site staff should still arrange an illness visit; this is not considered a protocol deviation.
- If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant, if possible, within 5 days after symptom onset or worsening for medical evaluation and nasopharyngeal swab collection. Clinical information will be collected to evaluate the severity of the case.
- All efforts must be made to collect a nasopharyngeal swab within 5 days of symptom onset for medical evaluation; however, if 5 days have elapsed since first symptom onset, swabs should still be collected as soon as possible, and this is not considered a protocol deviation.
- All participants who report symptoms or worsening of RSV-like illness will receive eDiary prompts to complete the PRO questionnaires (Part A only).

Respiratory disease will be defined by a new onset or worsening (> 24 hours) of one or more of any of the following:

- Rhinorrhea
- Nasal congestion
- Pharyngitis (sore throat)
- Cough
- New or increased wheezing
- New or increased shortness of breath
- Tachypnea (≥ 20 breaths per minute)
- New or increased sputum production or a change in the volume or character of sputum
- Fever (≥ 37.8°C [100.0°F])
- Chills
- Hoarseness

- Sinus pain
- Pleuritic chest pain

"New onset" will require at least a 14-day period free of symptoms or with baseline symptoms, to differentiate an episode from any prior acute illness. "Worsening" will require > 24 hours of worsening of a chronic symptom (eg, worsening cough in a person with a chronic cough) or the occurrence of additional new or intensified respiratory symptoms. When any participant is determined to have a new or worsening respiratory disease, the participant will be invited to have an unscheduled visit and will be evaluated (and tested, if RSV is suspected). During this visit (unscheduled visit), which will occur within 5 days, if possible, of symptom onset or worsening, the following assessments will be performed:

- Review and confirmation of the history of respiratory disease, including approximate date of onset or worsening of respiratory disease and solicitation of each of the above-listed symptoms. Participants will also be asked about exposure to individuals with known RSV infection.
- Vital signs measurements, including resting respiratory rate and oxygen saturation (on room air or the participant's basal level of chronic supplemental oxygen use), which will be captured as numerical values.
- Ascertainment of HRQoL using the EQ-5D-5L questionnaire at the time of RSV symptom start and subsequent measurement times (Part A only).
- Ascertainment of WPAI at 1 week and 2 weeks following start of RSV symptoms (Part A only).
- Ascertainment of any visits to nonstudy health care practitioner, including a healthcare visit by the participant, a mobile/home visit by a healthcare provider, or emergency room/urgent healthcare visit in response to the episode of respiratory disease.
- Ascertainment of hospital admission or prolongation of existing hospital stay in response to the episode of respiratory disease.
- Ascertainment of new concomitant medications (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from the respiratory disease.
- Collection of a specimen of upper respiratory secretions via nasopharyngeal swabs for detection of respiratory pathogens by RT-PCR.

Participants will continue to complete the eDiary for ascertainment of respiratory symptom status. Subsequently, the study staff will contact the participants weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications. This follow-up will occur regardless of whether the participant had a positive test for RSV.

Immunogenicity Assessments for Parts A and B:

Immunogenicity assessments will include the following:

- Serum neutralizing Ab level to RSV-A and RSV-B.
- Serum binding Ab level to the RSV pre and post fusion glycoprotein

(Part A only).

- Exploratory assays to characterize the immune responses to RSV or other respiratory viruses may be performed (Part A only).

Safety Assessments for Parts A and B:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following the study injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following the study injection (ie, the day of injection and 27 subsequent days).
- AEs leading to discontinuation from study participation from Day 1 through EOS or withdrawal from the study.
- MAAEs from Day 1 through EOS or withdrawal from the study.
- AESIs from Day 1 through EOS or withdrawal from the study.
- SAEs from Day 1 through EOS or withdrawal from the study.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.

Investigational Product, Dosage, and Route of Administration for Parts A and B:

The term "IP" refers to both mRNA-1345 vaccine and placebo administered in this study.

The mRNA-1345 is a lipid nanoparticle (LNP) dispersion of mRNA sequences encoding the RSV fusion glycoprotein stabilized in the prefusion conformation, formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000.

For the Phase 2 segment of Part A of the study, the mRNA-1345 vaccine will be provided as a sterile liquid for injection and will be a white to off-white dispersion, at a concentration of 0.4 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 8.6 mM sodium acetate at pH 7.5.

For the Phase 3 segment of Part A of the study and for the Part B substudy, mRNA-1345 vaccine will be provided as in the Phase 2 segment but at a concentration of 0.1 mg/mL in 20 mM Tris containing 87 mg/mL sucrose and 2.2 mM acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, which meets the criteria of the United States Pharmacopeia.

The IP (mRNA-1345 or placebo) will be administered as a 0.5-mL single IM injection on Day 1 to participants in both Phase 2 and Phase 3 segments of Part A of the study and on BD Day 1 to participants in the Part B substudy, according to the procedures specified in the mRNA-1345-P301 Pharmacy Manual.

Sample Size for Part A:

This Phase 2/3 study will plan to randomize approximately 37,000 participants (1:1 randomization ratio) to the mRNA-1345 or the placebo groups. Therefore, approximately 18,500 participants will be randomized to each group.

Power Calculation for the Primary Efficacy Endpoints

The sample size is driven by the total number of cases to demonstrate VE (mRNA-1345 vs. placebo) to prevent protocol-defined RSV-LRTD diseases.

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1345 and placebo, a total of 86 RSV-LRTD cases with 2 or more symptoms in the Per-protocol Efficacy (PPE) Set will provide at least 90% power to demonstrate VE, ie, rejecting the null hypothesis H^1_0: VE ≤ 20%, with 2 IAs at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a 1-sided type I error rate of 2.5%.

The total number of cases pertains to the PPE Set accruing within the period of 14 days post-injection up to 12 months post-injection. There are 2 planned IAs for this endpoint, which will be performed when at least 43 (50%) and when at least 74 (85%) cases of RSV-LRTD with 2 or more symptoms have been observed within the target total number of cases. Approximately 37,000 participants will be randomized with the following assumptions:

- The target VE against protocol-defined RSV-LRTD with 2 or more symptoms is 65%.
- An attack rate of 0.5% in the placebo arm for protocol-defined RSV-LRTD with 2 or more symptoms.
- Two IAs at approximately 50% and 85% of total target RSV-LRTD cases with 2 or more symptoms across the 2 study vaccination groups in the PPE Set, respectively.
- A dropout rate ~10% (not evaluable for the PPE Set).
- Type I error rate will be adjusted using the Pocock boundary.

If the IAs are conducted exactly at 50% and 85% of total targeted cases, the nominal 1-sided type I error rate will be 1.55%, 1.18%, and 0.91% at IA1, IA2, and the primary analysis, respectively.

In addition, the sample size, 37,000 participants and a total of 32 RSV-LRTD cases with 3 or more symptoms in the PPE Set will provide approximately 89% power to demonstrate VE, ie, rejecting the null hypothesis H^2_0: VE ≤ 20%, with 2 IAs at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a 1-sided type I error rate of 2.5%.

The total number of cases pertains to the PPE Set within the period of 14 days post-injection up to 12 months post-injection. There are 2 planned IAs for this endpoint, which will be performed when approximately 16 (50%) and 28 (85%) RSV-LRTD cases with 3 or more symptoms of the target total number of cases have been observed. This sample size calculation is based on the following assumptions:

- The target VE against protocol-defined RSV-LRTD with 3 or more symptoms is 80%.
- An attack rate of 0.2% in the placebo arm for protocol-defined RSV-LRTD with 3 or more symptoms.
- Two IAs at approximately at 50% and 85% of total target RSV-LRTD cases with 3 or more symptoms across the 2 study vaccination groups in the PPE Set, respectively.
- A dropout rate ~10% (not evaluable for the PPE Set).

- Type I error rate will be adjusted using the Pocock boundary.

It is expected the IA1 for both primary endpoints will be conducted at the same time, ie, IA1 will be conducted when at least 43 RT-PCR confirmed protocol-defined RSV-LRTD cases with 2 or more symptoms and at least 16 RT-PCR confirmed protocol-defined RSV-LRTD cases with 3 or more symptoms are observed in the PPE Set. Similarly, IA2 for both primary endpoints will be conducted at the same time.

Cases will be quantified (without unblinding) on an ongoing basis. If the targeted number of cases are not met in the original 37,000 participants, an extension of enrollment will be pursued. As the sample size recalculation will be performed without unblinding the study, no adjustment of the alpha for the primary analysis will be performed.

Power Calculation for the Key Secondary Efficacy Endpoints

For the key secondary endpoints, with approximately 18,500 participants per group, below tables provide power of demonstrating VE based on an attack rate of 2.0% for a first episode of RSV-ARD and a rate of 0.2% for a first hospitalization associated with RSV-ARD or RSV-LRTD, respectively, under different scenarios of true VE and VE criteria at a 1-sided type I error of 2.5% considering a ~10% ineligibility rate in the PPE Set. The study has at least 95% power to detect a VE = 50% against H^3_0: VE ≤ 20% to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection and approximately 89% power to detect a VE = 75% against H^4_0: VE ≤ 20% to prevent a first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

Power of Demonstrating Vaccine Efficacy to Prevent a First Episode of RSV-ARD

True VE	Placebo Attack Rate	VE to Prevent a First Episode of RSV-ARD	
		To Reject Null Hypothesis	Power
50%	2.0%	VE ≤ 30%	> 95%
55%			> 95%
60%			> 95%

Power of Demonstrating Vaccine Efficacy to Prevent a First Hospitalization Associated with RSV-ARD or RSV-LRTD

True VE	Placebo Hospitalization Rate	VE to Prevent Hospitalizations Associated with RSV-ARD or RSV-LRTD	
		To Reject Null Hypothesis	Power
75%	0.2%	VE ≤ 20%	90%
80%			95%
85%			> 95%

Sample Size for Part B Substudy (Select US Sites Only):

This substudy will plan to randomize approximately 1500 participants in a 2:1 randomization ratio to the mRNA-1345 or placebo groups. Therefore, approximately 1000 participants will be randomized to the mRNA-1345 group and 500 participants will be randomized to the placebo group.

With approximately 1000 participants randomized to mRNA-1345, the substudy has approximately 95% probability to observe at least 1 participant in the group with an AE at a true 0.3% AE rate.

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-A nAb at BD Day 29, compared with the GMT of RSV-A nAb at Primary Dose Day 29, using a paired t-test at a 2-sided alpha of 0.05. The assumptions are: the true GMT ratio (GMT of RSV-A nAb at BD Day 29 to Primary Dose Day 29) is 0.8, the standard deviation of the natural log-transformed titer is 1.5, with a noninferiority margin of 1.5.

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-B nAb at BD Day 29, compared with the GMT of RSV-B nAb at Primary Dose Day 29, using a paired t-test at a 2-sided alpha of 0.05. The assumptions are: the true GMT ratio (GMT of RSV-B nAb at BD Day 29 to Primary Dose Day 29) is 0.8, the standard deviation of the natural log-transformed titer is 1.5, with a noninferiority margin of 1.5.

The global power considering meeting both coprimary objectives is at least 90%.

Statistical Methods for Part A:

Statistical Hypothesis

There are 2 primary efficacy objectives in this study.

The first primary efficacy objective is to evaluate vaccine efficacy (VE) of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms.

The corresponding null hypothesis is that the VE of mRNA-1345 as compared to a placebo to prevent the occurrence of protocol-defined RSV-LRTD with 2 or more symptoms is ≤ 20% (ie, H^1_0: VE ≤ 20%). The VE is defined as the percent of reduction in the hazards of the primary endpoint (mRNA-1345 vs. Placebo). Equivalently, the null hypothesis is: $H^1$0: hazard ratio (HR) ≥ 0.8.

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1345 and placebo at a 1-sided 2.5% significance level.

The study will be considered to meet the first primary efficacy objective as long as the corresponding 2-sided (1 - 2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms rules out 20% at the time of analysis.

Once H^1_0 is rejected, the VE will be further evaluated for the second primary efficacy objective, evaluating VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms. The corresponding null hypothesis is that the VE of mRNA-1345 as compared to a placebo to prevent the occurrence of protocol-defined RSV-LRTD with 3 or more symptoms is ≤ 20% (ie, H^2_0: VE ≤ 20%). Equivalently, the null hypothesis is: H^2_0: hazard ratio (HR) ≥ 0.8.

The study will be considered to meet the second primary efficacy objective as long as the corresponding 2-sided (1 - 2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms rules out 20% at the time of analysis. Cases will be counted within the period of 14 days post-injection up to 12 months post-injection. The primary analysis population for efficacy will be the per-protocol (PP) Efficacy (PPE) Set.

Analysis Populations

Population	Description
Randomization Set	All participants who are randomized in the study, regardless of the participant's IP administration status. Participants will be included in the vaccination group to which they are randomized.
Full Analysis Set (FAS)	All randomized participants who receive any IP. Participants will be analyzed according to the vaccination group to which they are randomized.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS complete at least 1 visit or surveillance 14 days after the IP administration. The mITT Set will be the secondary population used for any immunogenicity analyses, disease cumulative incidence descriptions or efficacy estimates. Participants will be analyzed according to the vaccination group to which they are randomized. This set includes participants with major protocol violations.
Per-protocol Immunogenicity (PPI) Set	A randomly selected subset of participants in the FAS who receive the assigned IP dose according to protocol, have RSV immunogenicity titer results at baseline (prior to IP administration at timepoint of interest), at least 1 valid result after the IP administration, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined prior to database lock and unblinding. The PPI Set will be the primary population used for immunogenicity analyses, including exploration of immunologic correlates of risk. Participants will be analyzed according to the vaccination group to which they are randomized.
Per-protocol Efficacy (PPE) Set	All participants in the mITT Set who receive the assigned IP dose according to protocol, complete at least 1 visit or surveillance contact 14 days after the IP administration and have no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding. The PPE Set will be the primary population for efficacy analyses, for the description of RSV disease rates among placebo recipients, and for the exploratory estimation of vaccine efficacy against health outcomes associated with various RSV disease endpoints. Participants will be analyzed according to the vaccination group to which they are randomized.

Solicited Safety Set	All randomized participants who receive any IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the IP that they actually receive.
Safety Set	All randomized participants who receive any IP. The Safety Set will be used for all analyses of safety. Participants will be included in the vaccination group corresponding to the IP that they actually receive.

Statistical Analyses

The overall type I error rate for the primary endpoint at the IAs and the primary analysis is strictly controlled at 2.5% (1-sided) based on the Lan-DeMets spending function. The primary efficacy results that will be considered statistically significant after consideration of the strategy for controlling the type I error as described below. Statistical significance of the primary efficacy endpoints can be achieved at either of the IAs or at the primary analysis. A sequential/hierarchical testing procedure will be used to control type I error rate over the primary efficacy endpoints, key secondary efficacy endpoints, and selected secondary efficacy endpoints. Key secondary efficacy endpoints and selected secondary efficacy endpoints will only be tested at the planned analysis at 12 months, or final analysis, whichever is applicable, when both primary efficacy endpoints achieve statistical significance.

Efficacy Analyses

Analysis of Primary Efficacy Endpoints

To assess the primary efficacy endpoint of VE of mRNA-1345 in preventing the first occurrence of protocol-defined RSV-LRTD with 2 or more (or with 3 or more) symptoms within the period of 14 days post-injection up to 12 months post-injection, Cox proportional hazards regression model based on PPE Set will be used to estimate HR. The VE, ie, 1-HR (mRNA-1345 vs. placebo) will be estimated with a 2-sided (1-2 × adjusted alpha) × 100% CI and a 1-sided p-value for testing H^1_0: VE ≤ 20% or H^2_0: VE ≤ 20%.

The VE is defined as percent of reduction in the hazards of the primary endpoint (mRNA-1345 vs. placebo) and will be estimated using 1-HR estimand. A stratified Cox proportional hazard model with study vaccination group as a fixed effect and stratification factors for randomization as covariates will be used based on the PPE Set to estimate the HR (mRNA-1345 vs. placebo). The Efron's method will be used to handle ties.

For the primary efficacy endpoints, participants without RT-PCR confirmed protocol-defined RSV-LRTD will be censored at the last study assessment date. Potential intercurrent events may include: 1) early discontinuation or death unrelated to RSV-LRTD; and 2) early RSV-LRTD up to 14 days after study dose.

The study will be considered to meet the first primary efficacy objective as long as the corresponding 2-sided (1-2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more (or 3 or more) symptoms rules out 20% at the time of analysis.

The 1-sided adjusted alpha at the IAs and primary analysis will be 1.55%, 1.18%, and 0.91% at IA1, IA2, and primary analysis, respectively, with overall 1-sided alpha for the primary endpoint = 2.5%. The analysis of the second primary endpoint will be conducted similarly.

Analyses of the primary endpoints will be performed based on the mITT Set using the same methods described above.

Subgroup analysis of the t primary efficacy endpoints will be performed to assess consistency of VE.

To support the primary analysis, VE will also be estimated by 1 minus the ratio of incidence rates adjusting for person-time, and the 95% CI of VE will be computed using the exact method, conditional upon the total number of cases adjusting for person-time.

Farrington and Manning's score method (Farrington and Manning 1990) based on PPE Set will also be applied as a supportive analysis to estimate VE with a 2-sided Farrington and Manning score-based 95% CI. The VE is estimated by 1 minus the ratio of incidence rates (mRNA-1345 versus placebo).

Kaplan-Meier curves will be used to plot the estimated cumulative incidences over time by vaccination group.

Descriptive statistics for the mRNA-1345 and placebo groups will also be produced.

Details are provided in the statistical analysis plan (SAP).

Analysis of Key Secondary and Secondary Efficacy Endpoints

Similar analysis methods as used for the primary efficacy endpoints will be applied for key secondary efficacy endpoints.

Negative binomial regression will be used for estimating VE of mRNA-1345 to prevent all-cause LRTD and all-cause hospitalization cases which could occur multiple times during the selected observation period.

An analysis of covariance model with the vaccination group as explanatory variable, adjusting for the stratification factor at randomization, baseline value if applicable, will be used to assess the treatment effect for the total frailty score from baseline to 12 months and 24 months post-injection.

Other secondary efficacy endpoints will be analyzed in a similar way as the primary analysis for the primary efficacy endpoints. More details can be found in the SAP.

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 vaccination group.

Adverse Events

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, vital signs, and physical examination findings.

Unsolicited AEs will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used in this study for the collection and severity grading of solicited ARs.

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

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, AESIs, severe AEs, and AEs leading to discontinuation from the study will be summarized. Number of events of unsolicited AEs, SAEs, MAAEs, and AESIs 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.

Immunogenicity Analyses

The secondary immunogenicity endpoints will be analyzed using the PPI Set, by vaccination group, unless otherwise specified.

Data from immunogenicity assays will be summarized for each vaccination group using seroresponse rates (SRRs) and geometric means (GM) with 95% CIs, for each timepoint for which an assessment is performed.

For the immunogenicity endpoints, GM of specific Ab titers with corresponding 95% CI at each timepoint and geometric mean fold rise (GMFR) of specific Ab titers with corresponding 95% CI at each postbaseline timepoint over preinjection baseline at Day 1 will be provided by vaccination group. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For summaries of GMTs, Ab titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ, unless otherwise specified.

The SRR of RSV nAbs is defined as the proportion of participants with post-vaccination titers ≥ 4 × LLOQ if baseline is < LLOQ or a ≥ 4-fold increase from baseline if baseline is ≥ LLOQ. Proportion of participants with seroresponse will be provided with 2-sided 95% CI using the Clopper-Pearson method by postbaseline timepoint.

Further details, including the participant sampling plan, will be described in the SAP.

Exploratory Analyses

Exploratory endpoints evaluating VE will be assessed by similar analysis methods as used for the analysis of the primary efficacy endpoint.

Analyses of the remaining efficacy and immunogenicity exploratory endpoints will be described in the SAP.

Subgroup Analyses

If sufficient case numbers of the primary and key secondary endpoints in a subgroup (ie, age or risk factors for LRTD) are available, subgroup analysis may be performed.

Planned Analyses

Interim Analysis

Two IAs, 1 primary analysis, 1 potential analysis at 12 months, and 1 final analysis are planned.

1. The first IA will be performed when approximately 50% of the planned cases (at least 43 RSV-LRTD cases with 2 or more symptoms and at least 16 RSV-LRTD cases with 3 or more symptoms) have occurred.
2. The second IA will be performed when approximately 85% of the planned cases (at least 74 RSV-LRTD cases with 2 or more symptoms and at least 28 RSV-LRTD cases with 3 or more symptoms) have occurred.
3. The primary analysis will be performed when approximately 86 RSV-LRTD cases with 2 or more symptoms and at least 32 RSV-LRTD cases with 3 or more symptoms have occurred.
4. The analysis at 12 months may be conducted for some secondary and exploratory endpoints, as appropriate.
5. The final analysis will be performed when all participants have completed Month 24 follow-up.

Statistical Methods for Part B Substudy (Select US Sites Only):

Statistical Hypothesis

The 2 coprimary immunogenicity objectives aim to demonstrate noninferiority of the serum RSV A and RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose. These objectives are supported by 2 coprimary endpoints, comparing the RSV-A and RSV-B GMTs at BD Day 29 to the RSV-A and RSV-B GMTs at Primary Dose Day 29.

The corresponding null hypotheses are:

Null hypothesis H^{b1}_0: Immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-A nAb at BD Day 29, is inferior compared with the GMT of RSV-A nAb at Primary Dose Day 29. The first coprimary objective is considered met if noninferiority of the GMT of RSV-A nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the GMR rules out 0.667 [ie, LB > 0.667] using a noninferiority margin of 1.5). GMR is the ratio of GMT of RSV-A nAb at BD Day 29 to Primary Dose Day 29.

Null hypothesis H^{b2}_0: Immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-B nAb at BD Day 29, is inferior compared with the GMT of RSV-B nAb at Primary Dose Day 29. The second coprimary objective is considered met if noninferiority of the GMT of RSV-B nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the GMR rules out 0.667 [ie, LB > 0.667] using a noninferiority margin of 1.5). GMR is the ratio of GMT of RSV-B nAb at BD Day 29 to Primary Dose Day 29.

Analysis Populations

Population	Description
Randomization Set	All participants who are randomized in the Part B substudy, regardless of the participant's IP administration status. Participants will be included in the vaccination group to which they are randomized.
FAS	All Part B randomized participants who receive any IP. Participants will be analyzed according to the vaccination group to which they are randomized.

PP Set	All participants in the FAS who receive both the Part A and Part B assigned IP doses according to protocol, have RSV immunogenicity titer results at pre-Primary Dose (baseline) (prior to the primary IP administration), have at least 1 valid result at Primary Dose Day 29 and at BD Day 29, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined prior to database lock and unblinding. The PP Set will be the primary population used for immunogenicity analyses. Participants will be analyzed according to the vaccination group to which they are randomized.
Solicited Safety Set	All Part B randomized participants who receive any IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the IP that they actually receive.
Safety Set	All Part B randomized participants who receive any IP. The Safety Set will be used for all analyses of safety. Participants will be included in the vaccination group corresponding to the IP that they actually receive.

Statistical Analyses

Immunogenicity Analyses

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

The coprimary endpoints, the GMR of RSV-A nAb or RSV-B nAb titers at BD Day 29 to Primary Dose Day 29, will be estimated by back transforming the mean of the paired difference of RSV-A nAb or RSV-B nAb within the booster vaccination group on the logarithmic scale between BD Day 29 and Primary Dose Day 29. The 95% CI for the GMR will be based on the paired t-test of the log-transformed values then back transformed to the original scale for presentation. For each coprimary endpoint, the noninferiority of GMT at BD Day 29 will be demonstrated if the LB of 95% CI for the GMR is > 0.667. GMT and corresponding 95% CI for RSV-A nAb or RSV-B nAb titers at BD Day 29 will be summarized descriptively by vaccination group.

The SRR of RSV-A nAb or RSV-B nAb, is defined as the proportion of participants with post-BD titers ≥ 4 × LLOQ if baseline is < LLOQ or a

≥ 4-fold increase from baseline if baseline is ≥ LLOQ. Baseline value is defined as the most recent nonmissing immune measurements collected before the mRNA-1345 primary dose.

The secondary endpoints, SRR difference and 95% CI of RSV-A nAb or RSV-B nAb at BD Day 29 and at Primary Dose Day 29, will be estimated through a logistic model with repeated measure adjusted for the within-participant correlation. The noninferiority of SRR at BD Day 29 will be demonstrated if the LB of 95% CI for SRR difference is > -10%.

In addition, data from immunogenicity assays will be summarized for each vaccination group using SRR and GMT with 95% CIs, for each timepoint for which an assessment is performed.

For the immunogenicity endpoints, GMT of nAb titers with corresponding 95% CI at each timepoint and GMFR of specific Ab titers with corresponding 95% CI at each post-BD timepoint over pre-Primary Dose (baseline) will be provided by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For summaries of GMTs, 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, unless otherwise specified.

Proportion of participants with seroresponse will be provided with 2-sided 95% CI using the Clopper-Pearson method by postbaseline timepoint.

Further details, including the participant sampling plan, will be described in the SAP.

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 vaccination group.

Adverse Events

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, vital signs, and physical examination findings.

Unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used in this substudy for the collection and severity grading of solicited ARs.

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

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, AESIs, severe AEs, and AEs leading to discontinuation from the substudy will be summarized. Number of events of unsolicited AEs, SAEs, MAAEs, and AESIs will be reported in summary tables accordingly.

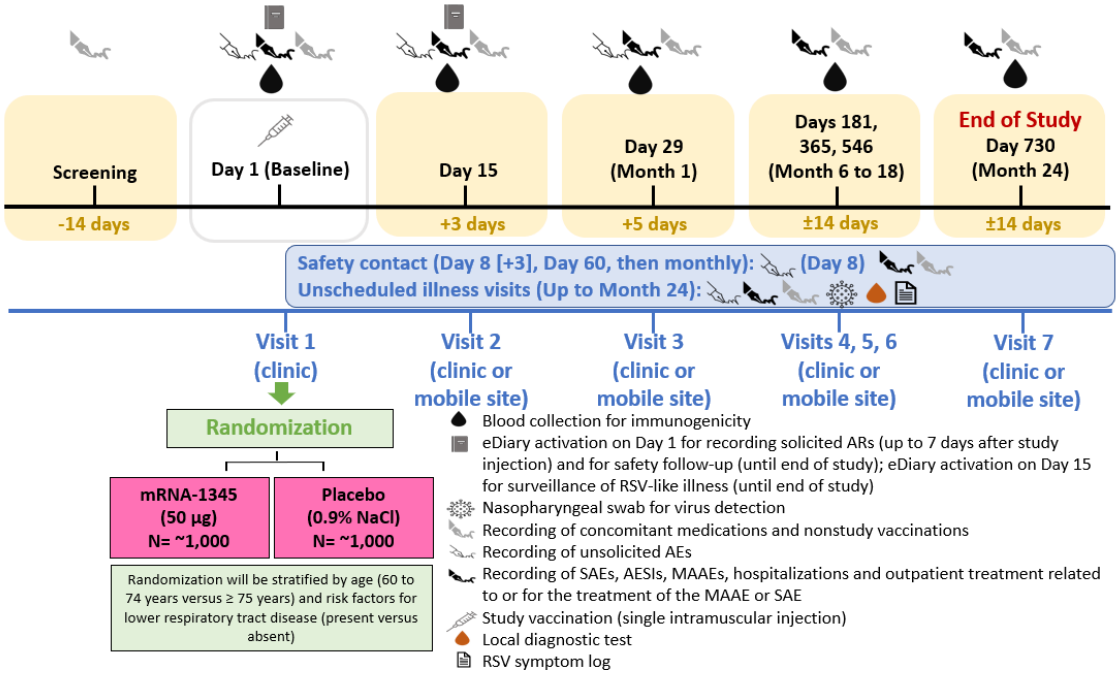
For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Exploratory Analyses

Analyses of exploratory endpoints will be described in the SAP.

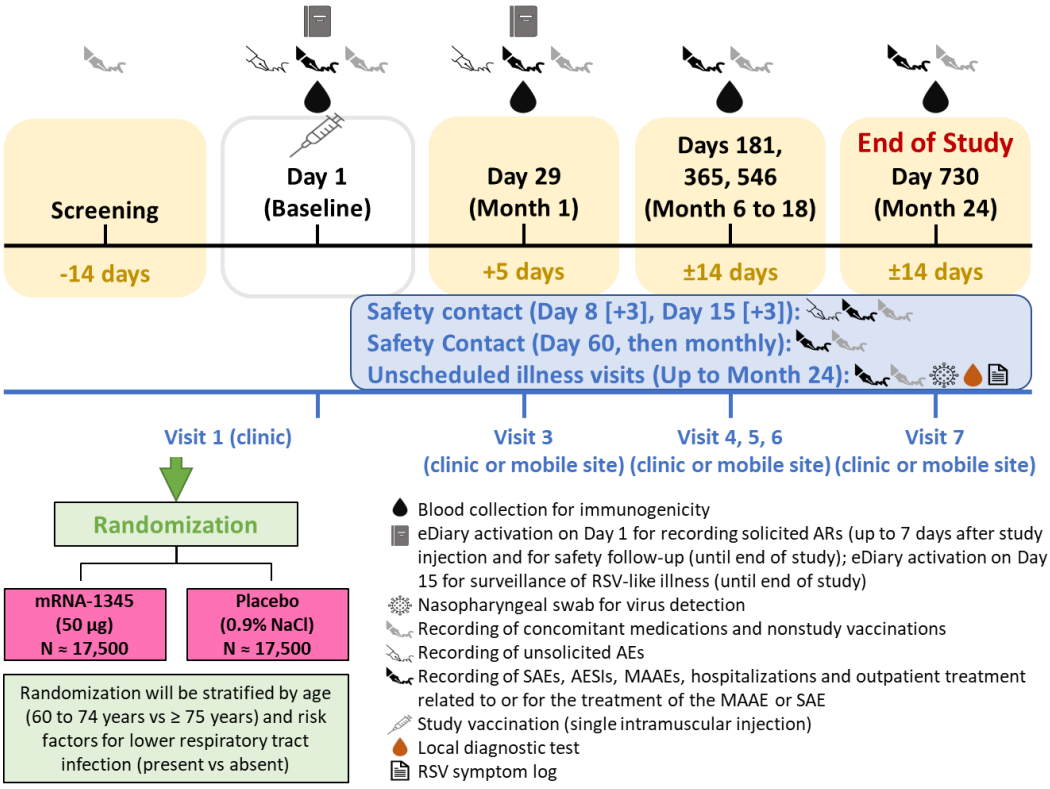
1.2. Schema

Figure 1: Study Schema – Part A Phase 2 Segment



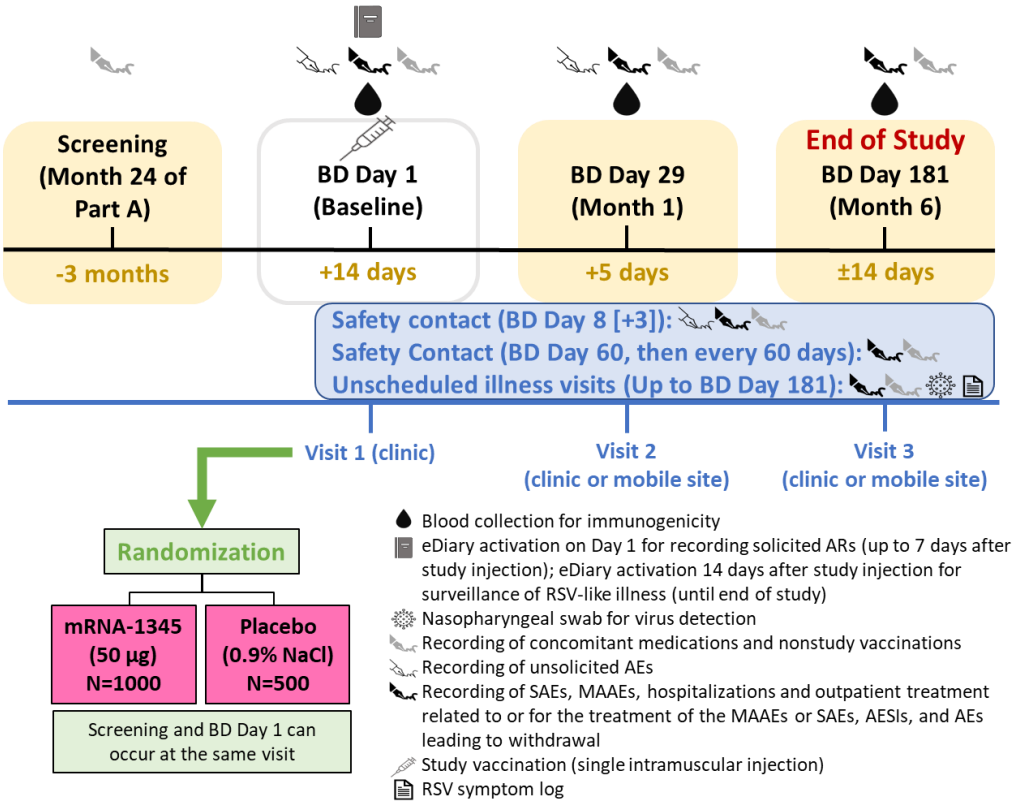
Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; eDiary = electronic diary; MAAE = medically-attended adverse event; NaCl = sodium chloride (normal saline); RSV = respiratory syncytial virus; SAE = serious AE.

Figure 2: Study Schema – Part A Phase 3 Segment



Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; eDiary = electronic diary; MAAE = medically-attended adverse event; NaCl = sodium chloride (normal saline); RSV = respiratory syncytial virus; SAE = serious AE.

Figure 3: Study Schema – Part B Substudy (Select US Sites Only)



Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; BD = booster dose; eDiary = electronic diary; MAAE = medically-attended adverse event; NaCl = sodium chloride (normal saline); RSV = respiratory syncytial virus; SAE = serious AE.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
2+ definition	RT-PCR confirmed protocol-defined RSV-LRTD with 2 or more symptoms
3+ definition	RT-PCR confirmed protocol-defined RSV-LRTD with 3 or more symptoms
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARD	acute respiratory disease
BD	booster dose
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendment
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DBP	Data Blinding Plan
DSMB	Data and Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG/EKG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EFS	Edmonton Frail Scale
EOS	end of study
ePRO	electronic patient-reported outcome
EQ-5D-5L	Five Level EuroQol 5-Dimension
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviation	Definition
GCP	Good Clinical Practice
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	healthcare practitioner
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin
IM	intramuscular
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IST	Internal Safety Team
LB	lower bound
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract illness
LTFU	lost to follow-up
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	modified intent-to-treat

Abbreviation	Definition
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per-protocol
PPE	per-protocol efficacy
PPI	per-protocol immunogenicity
PreF	prefusion conformation
PostF	postfusion conformation
PRO	patient-reported outcome
QA	quality assurance
QoL	quality of life
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV-A	respiratory syncytial virus subtype A
RSV-ARD	respiratory syncytial virus-associated acute respiratory disease
RSV-B	respiratory syncytial virus subtype B
RSV-LRTD	respiratory syncytial virus-associated lower respiratory tract disease
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
SoE	Schedule of Events
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
Th1	T helper 1
ULOQ	upper limit of quantification
US	United States
USP	United States Pharmacopeia
VE	vaccine efficacy
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire

2. INTRODUCTION

2.1. Study Rationale

This study is divided into Part A (Section 3) and the Part B substudy (Section 4).

Part A is a Phase 2/3, randomized, observer-blind, placebo-controlled, multicenter study that will be conducted in multiple countries. The primary purpose of the Phase 2 segment of Part A of the study is to confirm the safety of mRNA-1345 vaccine in adults ≥ 60 years of age for initiation of the large-scale Phase 3 segment of Part A of the study. The primary purpose of the Phase 3 segment of Part A of the study is to establish the safety and efficacy of mRNA-1345 vaccine in adults ≥ 60 years of age in support of licensure.

Part B is a Phase 3, randomized, observer-blinded, placebo-controlled, multicenter substudy to evaluate the safety, tolerability, and immunogenicity of revaccination with a single 50 µg booster dose (BD) of mRNA-1345 in participants who received a primary dose of mRNA-1345 in Part A. For the purposes of this substudy, the terms revaccination and booster are used interchangeably. The Part B substudy will be conducted at select US sites only. Administration of a BD may increase respiratory syncytial virus (RSV)-specific neutralizing antibodies (nAbs), which may translate to potential added protection from RSV-related disease.

2.2. Background and Overview

All-cause lower respiratory tract infection (LRTI; including pneumonia) represents a substantial burden of illness in older adults. It is estimated that LRTIs caused approximately 1.27 million deaths (95% CI: 1.15-1.34 million) in older adults across 195 countries in 2015 (Shi et al 2020). RSV has been identified as an important etiology of acute respiratory disease (ARD) in adults, causing 7.80% of symptomatic respiratory infections in seasonal studies among those ≥ 60 years in developed countries (Nguyen-Van-Tam et al 2022). In 2019, RSV is estimated to have caused 5.2 million acute respiratory infections, 470,000 hospitalizations, and 33,000 in-hospital deaths in high-income countries among adults aged ≥ 60 years (Savic et al 2023). In the US, the Centers for Disease Control and Prevention (CDC) estimates that RSV infection results in 60,000 to 160,000 hospitalizations and 6000 to 10,000 deaths per year in older adults (CDC 2023b; CDC 2023c). Studies conducted in the US and Japan indicate that RSV may contribute to between 3% and 15% of community-acquired pneumonia, 9% to 10% of hospital admissions for acute cardiorespiratory diseases, and approximately 6500 excessive deaths during seasonal peaks in older adults (Hansen et al 2022; Katsurada et al 2017; Murata and Falsey 2007; Lee et al 2013). The annual incidence of RSV infection is estimated to be 3% to 7% in healthy older adults and 4% to 10% in high-risk adults, based on prospective cohort studies conducted in the US and Europe (Falsey et al 2005, Korsten et al 2021).

RSV is a single-stranded, enveloped ribonucleic acid (RNA) virus that belongs to the pneumovirus family. The fusion glycoprotein of the RSV envelope is a conserved target of protective nAbs for both subtypes of RSV: RSV-A and RSV-B. Passive immunotherapy with palivizumab, a monoclonal antibody (Ab) that targets the fusion protein, successfully prevents RSV-associated lower respiratory tract disease (RSV-LRTD) in infants and children who were at high risk of severe outcomes, such as those with chronic heart or lung conditions (AAP COID and AAP Bronchiolitis Guidelines Committee 2014). On 17 Jul 2023, the US FDA approved the

monoclonal Ab, nirsevimab, for use in infants and children to protect against medically-attended RSV disease (FDA 2023). On 3 Aug 2023, the Advisory Committee on Immunization Practices voted to recommend nirsevimab for 1) all infants younger than 8 months born during or entering their first RSV season, and 2) all infants aged 8 through 19 months who are at increased risk of severe disease and entering their second RSV season (CDC 2023a).

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

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

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

2.2.1. Nonclinical Studies

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

In an in vivo dose-response study, the immunogenicity of mRNA-1345 was evaluated in female BALB/c mice at 4 dose levels (0.1, 0.2, 1, and 5 µg) after intramuscular (IM) injections on Day 1 and Day 22. mRNA-1345 induced a dose-dependent RSV neutralizing and binding Ab response in mice. mRNA-1345 induced a balanced immunoglobulin (IgG)2a:IgG1 response, indicating a T helper 1 (Th1) response.

In addition, in a non-Good Laboratory Practice immunogenicity and safety study in Sprague-Dawley rats, mRNA-1345 was administered at clinically relevant dose levels of 15, 50, and 100 µg/dose via IM injections on Day 1 and Day 22. RSV nAbs were detected in the serum of all animals administered mRNA-1345 and a dose-dependent nAb response was observed. Administration of mRNA-1345 was well tolerated up to 100 µg/dose. There were no mRNA-1345-related mortalities or changes in body weight or body weight gains. Clinical signs consisted of transient local effects of edema and impaired limb functions at the injection site. Changes in clinical pathology parameters were consistent with an inflammatory response in addition to a mild liver effect in individual animals.

A detailed review of nonclinical experience with mRNA-1345 vaccine is provided in the investigator's brochure (IB).

2.2.2. Clinical Studies

The mRNA-1345 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study (NCT04528719). The Phase 1 study is an observer-blind, placebo-controlled, dose escalation study of mRNA-1345 in healthy younger adults aged 18 to 49 years, women of child-bearing potential aged 18 to 40 years, healthy older adults aged 65 to 79 years, Japanese older adults aged ≥ 60 years, and RSV-seropositive children aged 12 to 59 months. Five dose levels of mRNA-1345 are being evaluated in the Phase 1 study: first 50 µg, 100 µg, and 200 µg in 100 healthy younger adults aged 18 to 49 years; then 12.5 µg, 25 µg, and 50 µg in 180 women of child-bearing potential; 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg in 325 healthy older adults aged 65 to 79 years (100-µg dose level in Japanese healthy older adults aged ≥ 60 years); and 15 µg and 30 µg in approximately 38 RSV-seropositive children aged 12 to 59 months. As of April 2022 and analyzed per study protocol, preliminary interim results from approximately 300 participants in the mRNA-1345 P101 older adult cohorts revealed that one dose of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg of mRNA-1345 was generally well tolerated up to 6 months (Day 169) after the first vaccination (mRNA-1345-P101 Interim Analysis 2022). There was no apparent association between unsolicited AEs and mRNA-1345 or dose level. A single mRNA-1345 injection of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg was immunogenic: it increased RSV-A and RSV-B neutralizing antibody titers, as well as prefusion (preF)- and postfusion (PostF)-binding antibodies. In general, the titers were lowest with 12.5 µg, similar for 25 µg, 50 µg, and 100 µg, and highest for 200 µg. Additional information about the mRNA-1345-P101 study and updated results can be found in the IB.

The 50-µg dose, administered as a single 0.5 mL IM injection, was selected for Phase 2/3 evaluation in older adults based on the safety, tolerability, and immunogenicity profile from the preliminary and interim analyses of the mRNA-1345-101 Phase 1 data in older adult cohorts (see IB). These data were assessed in conjunction with the chemistry, manufacturing, and control quality control strategy to ensure an effective dose through end of expiry at a given dose level.

The effective dose is a measure of potency and is defined by the nominal dose multiplied by the percent purity of the vaccine at administration. Percent purity is a critical quality attribute because of the potential impact of lower purity on efficacy. The percent purity of mRNA-1345 drug product is expected to decrease throughout the intended storage and use conditions with an end of shelf-life specification of [redacted]. Therefore, to maintain an effective dose through the end of expiry specific to mRNA-1345, the Sponsor has selected a nominal dose that is twice the dose that first reaches the antibody titer plateau. Because the first dose level to reach the antibody titer plateau is 25 µg, the Sponsor has selected a dose of 50 µg. For the Phase 3 clinical study, mRNA-1345 drug product will be administered with a percent purity profile that is representative of the commercial intended storage and use conditions.

The results from the mRNA-1345-P101 study will be used to support and inform subsequent evaluations of the mRNA-1345 vaccine in future clinical studies.

Results from a prespecified IA of the current study (mRNA-1345-P301; data cutoff 30 Nov 2022) demonstrate that the primary efficacy objectives were met, including:

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

2.3. Benefit/Risk Assessment

2.3.1. Potential Benefits of Study Participation

Although the VE of mRNA-1345 against RSV-LRTD was demonstrated in Part A (Section 2.2.2), participants who receive a BD of 50 µg of mRNA-1345 in Part B may or may not directly benefit from vaccination as the efficacy of the mRNA-1345 booster is yet to be established.

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

2.3.2. Risks from Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 60 minutes after study injection.

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

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. These local adverse reactions (ARs) typically include 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 vaccination.

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

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

There have been very rare (< 1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with coronavirus disease 2019 (COVID-19) mRNA vaccines. The majority of the cases have been reported in adolescents and young males, within 7 to 14 days after the second or subsequent doses of the vaccine. These are typically mild cases, and individuals tend to recover within a short time following conservative treatment (including rest, NSAIDs, and/or colchicine). Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021). It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of other non-COVID mRNA vaccines.

2.3.3. Overall Benefit/Risk Conclusion

The proposed Phase 2/3 clinical study (Part A) evaluating mRNA-1345 in adults ≥ 60 years of age is supported by nonclinical safety and immunogenicity studies and a Phase 1 clinical study. The Phase 3 clinical substudy (Part B) is supported by safety and efficacy data from Part A.

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

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

Taking into account the measures used to minimize the risk to individuals participating in this study and oversight by an IST and an independent DSMB, the potential risks to the participants are justified by the potential benefits linked to the development of the RSV vaccine in older adults.

3. PART A

3.1. Objectives and Endpoints (Part A)

3.1.1. Primary Objectives and Endpoints (Part A)

The primary objectives and endpoints for Part A are given in Table 1.

Table 1: Primary Objectives and Endpoints (Part A)

Primary Objectives	Primary Endpoints
Safety Objective	**Safety Endpoints**
• To evaluate the safety and tolerability of the mRNA-1345 vaccine.	• Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) up to 7 days post-injection. • Unsolicited adverse events (AEs) up to 28 days post-injection. • Medically-attended adverse events (MAAEs), adverse events of special interest (AESIs), serious adverse events (SAEs), and AEs leading to withdrawal up to 24 months post-injection.
Efficacy Objective	**Efficacy Endpoints**
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-associated lower respiratory tract disease (RSV-LRTD) as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection. • Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically-attended adverse event; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SAE = serious adverse event.

3.1.2. Secondary Objectives and Endpoints (Part A)

3.1.2.1. Key Secondary Objectives and Endpoints (Part A)

The key secondary efficacy objectives and endpoints for Part A are given in Table 2.

Table 2: Key Secondary Efficacy Objectives and Endpoints (Part A)

Key Secondary Efficacy Objectives	Key Secondary Efficacy Endpoints
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-ARD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection.

Key Secondary Efficacy Objectives	Key Secondary Efficacy Endpoints
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

Abbreviations: RSV-ARD = respiratory syncytial virus-associated acute respiratory disease;
RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease.

3.1.2.2. Other Secondary Objectives and Endpoints (Part A)

The other secondary efficacy objectives and endpoints for Part A are given in Table 3.

Table 3: Other Secondary Objectives and Endpoints (Part A)

Secondary Objectives	Secondary Endpoints
Efficacy Objectives	**Efficacy Endpoints**
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause hospitalizations as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent all-cause LRTD within the period of 14 days post-injection up to 12 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection. • Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo by RSV subtype.	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD by RSV subtype A and RSV subtype B.
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.	• Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection.

Secondary Objectives	Secondary Endpoints
• To evaluate the efficacy of a single dose of mRNA-1345 vaccine on the change from baseline in frailty status at 12 months and 24 months.	• Change in total frailty score from baseline to 12 months and 24 months post-injection, using the EFS.
Immunogenicity Objective	**Immunogenicity Endpoints**
• To evaluate the Ab response to a single dose of mRNA-1345 vaccine from baseline up to 24 months post-injection.	• GMT of serum RSV neutralizing Abs and GMC of serum RSV binding Abs at prespecified study timepoints from baseline up to 24 months post-injection. • SRR in RSV neutralizing Abs up to 24 months post-injection. • GMFR from baseline at prespecified study timepoints up to 24 months post-injection. • Proportion of participants with ≥ 2-fold increase in Ab titer from baseline at prespecified study timepoints up to 24 months post-injection.

Abbreviations: Ab = antibody; EFS = Edmonton Frail Scale; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SRR = seroresponse rate.

3.1.3. Exploratory Objectives (Part A)

The exploratory objectives for Part A are as follows:

- To evaluate immune response biomarkers after dosing with mRNA-1345 vaccine as potential correlates of protection or risk of RSV disease.
- To conduct additional analyses relating to further understanding of infection and disease associated with RSV and related pathogens, including analyses related to the immunology of vaccination, viral infection, and clinical conduct.
- To describe the effect of immunization with mRNA-1345 vaccine on the prevention or mitigation of RSV-LRTD and all-cause LRTD with at least 1, 2, 3, 4, or 5 symptoms or signs of lower respiratory tract involvement.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause hospitalizations as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause ARD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-ARD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.

- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause LRTD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause ARD as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on level of care required for daily living.
- To evaluate the effect of a single dose of mRNA-1345 vaccine on prevention of exacerbations of congestive heart failure (CHF) up to 12 months and 24 months post-injection.
- To evaluate the effect of a single dose of mRNA-1345 vaccine on prevention of exacerbations of chronic obstructive pulmonary disease (COPD) up to 12 months and 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-LRTD by baseline frailty status.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-ARD by baseline frailty status.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-LRTD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease, if feasible and relevant.
- To describe the effect of a single dose of mRNA-1345 vaccine on the number of participants with first episode of RSV-ARD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease, if feasible and relevant.
- To describe the effect of a single dose of mRNA-1345 vaccine on death from all causes at 12 months and 24 months post-injection.
- To describe the effect of a single dose of mRNA-1345 vaccine on the change from baseline in health-related quality of life (HRQoL) at 12 months and 24 months using the 5 level EuroQol 5 Dimension (EQ-5D-5L) utility index scores.
- To describe the effect of a single dose of mRNA-1345 vaccine on HRQoL for participants with RSV-LRTD or RSV-ARD using the EQ-5D-5L utility index scores.
- To describe the effect of a single dose of mRNA-1345 vaccine on Work Productivity and Activity Impairment Questionnaire (WPAI) impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with RSV-LRTD or RSV-ARD.
- To describe the effect of a single dose of mRNA-1345 vaccine on the prevention or mitigation of the following:

  - Healthcare encounters (medical attendance and hospitalizations) associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD
  - Duration of hospital encounters associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD
  - Prescriptions for medications including antibiotics associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD.
- To explore the feasibility of linking patient-level data to real-world electronic health databases to extend the duration of monitoring for healthcare utilization or encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes (US sites only).

3.1.3.1. Economic Analysis (Part A)

A separate economic analysis is planned to estimate the impact of vaccination with mRNA-1345 on QoL-adjusted survival and on healthcare costs in real-world practice in one or more geographies. If performed, this analysis would use information on clinical, QoL, and resource use outcomes collected within the study to estimate QoL and costs to a healthcare payer comparing a strategy of vaccination with mRNA-1345 to no vaccination. This analysis would be conducted under a separate analysis plan and be intended for submission to health technology assessment and payer audiences to support use of mRNA-1345 following launch.

3.1.3.2. Linkage to Real-World Data (Part A)

To further extend the duration of monitoring for medical product utilization or healthcare encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes, a subset of consenting participants at US sites may be enrolled into substudies or subanalyses that allow linkage or tokenization to these systems.

3.1.4. Study Endpoint Definitions (Part A)

The definitions of the efficacy endpoints for Part A are given in Table 4.

Table 4: Efficacy Endpoint Definitions (Part A)

Endpoint	Definition
RSV-LRTD with 2 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.

Endpoint	Definition
RSV-LRTD with 3 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 3 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.
RSV-ARD	RT-PCR-confirmed RSV infection **PLUS** an acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93%, or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-ARD.
All-cause LRTD	New or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause LRTD.
All-cause ARD	An acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause ARD.

Abbreviations: ARD = acute respiratory disease; LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; RT-PCR = reverse transcription polymerase chain reaction.

Note: The source of the clinical symptomology that supports the case definition can be participant reported and/or from a clinical assessment.

3.2. Study Design (Part A)

3.2.1. General Design (Part A)

This is a Phase 2/3, randomized, observer-blind, placebo-controlled, case-driven study to evaluate the safety and efficacy of mRNA-1345 vaccine as compared with placebo in adults ≥ 60 years of age. Immunogenicity of mRNA-1345 vaccine will be characterized and investigation for correlates of risk will be undertaken. The study will be conducted in 2 phases: Phase 2 and Phase 3 (see details in Section 3.2.1.1 and Section 3.2.1.2, respectively) under the oversight of an independent DSMB. The study schemas are given in Figure 1 and Figure 2 for Phase 2 and Phase 3 segments, respectively. Phase 2 will be conducted in the US only. The Phase 3 segment is a multinational study which is planned to be conducted in the following countries: Argentina, Australia, Bangladesh, Belgium, Canada, Chile, Colombia, Costa Rica, Finland, Germany, Japan, Mexico, New Zealand, Panama, Poland, Singapore, South Africa, South Korea, Spain, Taiwan, the United Kingdom, and the US to assure adequate participant accrual in advance of the RSV seasons.

Each phase of the study will have a screening period (up to 14 days before study injection), a single dose of study injection (Day 1), and a follow-up period (up to 24 months after study injection). The study duration will be approximately 25 months for each participant, except for a subset of participants at select US sites who may complete the Day 730 (Month 24) visit up to 3 months (90 days) early to allow screening activities for the Part B substudy. All participants will complete up to 8 scheduled visits at the clinic or mobile site, including Screening, Day 1, Day 15 (for Phase 2), Day 29, Day 181, Day 365, Day 546, and Day 730. All participants will have a safety contact (via telephone, email, text message, or other electronic means) on Day 8, Day 15 (for Phase 3), Day 60, and then monthly (ie, every 30 days). The Schedules of Events (SoEs) for the Phase 2 and Phase 3 segments of the study are given in Table 20 and Table 21, respectively. Details about handling of missed or delayed visits and other participant encounters are provided in Section 3.6.

Each participant will receive a single dose of study injection (50 µg mRNA-1345 or placebo) as a 0.5-mL IM injection on Day 1.

Participants will be given and trained to use an electronic diary (eDiary) on the day of study injection (Day 1) to report solicited ARs and all other AEs for 7 days after the study injection.

Active and passive surveillance will be conducted for RSV-like illness and exposure to individuals with known RSV, also using the eDiary, starting from Day 15 (14 days after the study injection) until Day 730. See Section 3.6.1.3 for symptoms of respiratory disease that will be surveyed and for details about eDiary prompts and unscheduled visits. If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant. The unscheduled visit will be performed within 5 days, if possible, after symptom onset or worsening, for medical evaluation and nasopharyngeal swab collection. All efforts must be made to collect a nasopharyngeal swab within 5 days of symptom onset for medical evaluation; however, if 5 days have elapsed since first symptom onset, swabs should still be collected as soon as possible, and this is not considered a protocol deviation. If a participant reports RSV-like symptoms prior to the active and passive surveillance period (which starts on Day 15), the site staff should still arrange an illness visit; this is not considered a protocol

deviation. All participants who report symptoms of RSV-like illness will receive eDiary prompts to complete PRO questionnaires (Table 20 and Table 21).

Safety contacts (Section 3.6.2.1) and eDiary safety prompts (Section 3.6.2.2) will be performed throughout the study and are intended to capture SAEs, MAAEs, hospitalizations and outpatient treatments related to or for the treatment of the MAAEs or SAEs, AESIs, AEs leading to withdrawal, concomitant medications associated with these events, and/or receipt of nonstudy vaccinations. If an eDiary prompt results in the identification of a relevant safety event, a follow-up safety contact will be triggered, and an unscheduled visit may be performed.

All participants will be assessed for safety, efficacy, and immunogenicity endpoints up to 24 months after the study injection. See the SoEs (Table 20 and Table 21) for the frequency and timing of safety, efficacy, and immunogenicity assessments.

Participants will be considered to have completed the study if they complete the final visit at Day 730 (Month 24), 24 months following the receipt of study injection. The EOS is defined as completion of the last visit of the last participant in the study or last scheduled procedure as shown in the SoEs (Table 20 and Table 21) for the last participant in the study globally.

Except for appropriately delegated unblinded pharmacists, vaccine administrators, clinical study managers, and monitors, all personnel involved in the conduct of the study will remain blinded to individual vaccination assignment until planned study unblinding (details can be found in Section 3.4.2.8.1 and the study-specific Data Blinding Plan [DBP]).

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

The study design elements specific to the Phase 2 and Phase 3 segments of the study are explained in Section 3.2.1.1 and Section 3.2.1.2, respectively.

3.2.1.1. Phase 2 Segment (Part A)

In the Phase 2 segment (US sites only), approximately 2000 participants will be randomly assigned to receive a single injection of 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Assignment will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent) (Section 3.4.2.1.1).

See Table 5 for the summary of enrollment in Phase 2 segment.

Table 5: Phase 2 Segment – Summary of Enrollment (Part A)

Age Stratum	**Stratification (Through IRT)** [a]		**Target Composition of Participants**	
	N ~1000 50 µg mRNA-1345	**N ~1000 Placebo**		
60 to 74 years	80%	80%	60-69 years	60%
			70-74 years [b]	20%
≥ 75 years	20%	20%	75-79 years [b]	10%
			≥ 80 years [b]	10%
Total	~2000[c]			

Abbreviations: IRT = interactive response technology; LRTD = lower respiratory tract disease.
Note: All participants will receive a single dose of the study injection (mRNA-1345 or placebo) on Day 1.

a. Randomization will also be stratified by risk factors for LRTD (present versus absent).
b. The study will target enrollment of approximately 30% of participants 70 to 79 years of age and approximately 10% of participants ≥ 80 years of age.
c. The final sample size of the Phase 2 segment will depend on real-time local surveillance of RSV circulation external to the study.

There will be safety data reviews at predefined intervals throughout the study. The safety reviews will be performed by both a blinded IST and an independent unblinded DSMB according to a specified monitoring plan outlined in a charter. The IST will comprise members not directly involved in the study. The DSMB will be composed of external independent subject matter experts and an unblinded statistician. The IST will conduct ongoing blinded safety reviews throughout the conduct of the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB will conduct unblinded reviews of safety data on a periodic basis as defined in a DSMB charter or as otherwise requested by the study team.

Final sample size of the Phase 2 segment will depend on real-time local surveillance of RSV circulation. The DSMB will review the Day 29 safety data from the first 400 participants who receive the study injection while further enrollment in the Phase 2 segment remains ongoing based on RSV surveillance information. Enrollment in the Phase 2 segment may expand up to 2000 participants if RSV surveillance data that are external to this study demonstrate a rise in RSV cases in a given region. No more than 2000 participants will be enrolled while the DSMB is reviewing the safety data from the Phase 2 segment of the study.

Participants in the Phase 2 segment will contribute to the planned Phase 3 analyses in a continuous Phase 2/3 study design.

3.2.1.2. Phase 3 Segment (Part A)

Enrollment in Phase 3 segment of the study will be triggered by the DSMB review of the Day 29 safety data from the first 400 participants in the Phase 2 segment of the study. In the Phase 3 segment, approximately 35,000 participants will be randomly assigned to receive a single injection of either 50 µg of mRNA-1345 vaccine or a placebo in a 1:1 randomization ratio. Assignment will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent) (Section 3.4.2.1.1).

See Table 6 for the summary of enrollment in Phase 3 segment.

Table 6: Phase 3 Segment – Summary of Enrollment (Part A)

<table>
<tr><th>Age Stratum</th><th colspan="2">Stratification (Through IRT) [a]</th><th colspan="2" rowspan="2">Target Composition of Participants</th></tr>
<tr><th></th><th>N ~17,500
50 µg mRNA-1345</th><th>N ~17,500
Placebo</th></tr>
<tr><td rowspan="2">60 to 74 years</td><td rowspan="2">80%</td><td rowspan="2">80%</td><td>60-69 years</td><td>60%</td></tr>
<tr><td>70-74 years [b]</td><td>20%</td></tr>
<tr><td rowspan="2">≥ 75 years</td><td rowspan="2">20%</td><td rowspan="2">20%</td><td>75-79 years [b]</td><td>10%</td></tr>
<tr><td>≥ 80 years [b]</td><td>10%</td></tr>
<tr><td>Total</td><td colspan="4">~35,000[c]</td></tr>
</table>

Abbreviations: IRT = interactive response technology; LRTD = lower respiratory tract disease.

Note: All participants will receive a single dose of the study injection (mRNA-1345 or placebo) on Day 1.

[a.] Randomization will also be stratified by risk factors for LRTD (present versus absent).

[b.] The study will target enrollment of approximately 30% of participants 70 to 79 years of age and approximately 10% of participants ≥ 80 years of age.

[c.] The final sample size of the Phase 3 segment will depend on real-time local surveillance of RSV circulation external to the study and the sample size of the Phase 2 segment.

This is a case-driven study and thus final sample size of the Phase 3 segment will depend on real-time local surveillance of RSV circulation external to the study and the sample size of the Phase 2 segment. The total study sample size including the participants in Phase 2 and Phase 3 segments of the study will be approximately 37,000.

If the prespecified criteria for early efficacy are met at the time of any IA or overall efficacy at the primary analysis, a final study report describing the safety and efficacy of mRNA-1345 will be prepared based on the data available at that time. In the event that success criteria are met at the time of either IA or when the total number of cases toward the primary endpoint have accrued, participants will continue to be followed in a blinded fashion until Month 24 to enable assessment of long-term VE.

Participants in both the Phase 2 and the Phase 3 segments will contribute to the planned safety, efficacy, and immunogenicity analyses.

3.2.2. Scientific Rationale for Study Design (Part A)

While COVID-19 related social-distancing interventions have led to a substantial reduction in RSV circulation in 2020/2021 (Gomez et al 2021), epidemiologic simulations suggest large and potentially off-season rebounds in RSV illness after relaxation of these interventions (Baker et al 2020). In this setting of an unclear start time of a potentially large RSV rebound season in the autumn of 2021, the conduct of an mRNA-1345 pivotal efficacy study in older adults could facilitate case capture and increase the feasibility of the study. The protocol is thus written to permit the flexibility of increasing enrollment during the Phase 2 segment of the study, should RSV surveillance indicate a strong rebound of illness burden.

This Phase 2/3 study was designed to be a randomized, stratified, observer-blind, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of mRNA-1345 RSV vaccine compared with placebo in adults ≥ 60 years of age who are, by virtue of their age, considered to be at a higher risk for RSV-associated morbidity and mortality. Ideally, participant recruitment in both phases of the study will occur prior to when RSV is expected to begin circulating. The Sponsor will use the following approaches for RSV surveillance to inform participant enrollment:

1. **Near real-time approach:** Identify the peak of RSV activity and monitor the decline of RSV activity until it reaches low levels of circulation using near real-time surveillance data relevant to the geography of the study sites. Enroll most of the participants during low levels of RSV activity so they are fully vaccinated when RSV activity begins to increase according to the near real-time surveillance data. Enrollment is reduced or ends around the time RSV activity peaks.
2. **Historical approach:** Start majority of study enrollment up to 6 months before the historical start of the RSV season and reduce or end study enrollment around the time the

historical RSV season peaks, referencing the most robust historical surveillance data for a particular geographic area.

The precise timing and pace of enrollment may accelerate or decrease based on anticipated seasonality or geography. Robust RSV circulation may reduce the number of total participants that the Sponsor will need to enroll to reach the target number of RSV cases and also increase the speed of the overall study.

The mRNA-1345 vaccine is being developed to prevent respiratory disease resulting from RSV infection. This Phase 2/3 study is designed to primarily evaluate the clinical safety and efficacy of mRNA-1345 to prevent RSV-LRTD for up to a year after single vaccination with mRNA-1345. The immunogenicity and VE to prevent RSV-LRTD and RSV-ARD up to 2 years after single vaccination with mRNA-1345 are secondary endpoints.

3.2.3. Choice of Dose and Control Product (Part A)

The 50-µg dose of mRNA-1345 was selected for this study based on the mRNA-1345-P101 safety and immunogenicity study data (see IB).

There is no licensed RSV vaccine currently available to serve as a reference control; therefore, 0.9% sodium chloride (normal saline) injection (United States Pharmacopeia [USP] or equivalent) will be used as a placebo control.

3.2.4. End of Study Definition (Part A)

Participants will be considered to have completed Part A of the study if they complete the final visit at Day 730 (Month 24), 24 months following the receipt of study injection.

The EOS is defined as completion of the last visit of the last participant in the study or last scheduled procedure as shown in the SoEs (Table 20 and Table 21) for the last participant in the study globally.

3.3. Study Population (Part A)

The study population will consist of adults ≥ 60 years of age with or without underlying medical conditions. The inclusion and exclusion criteria for the study are listed in Section 3.3.1 and Section 3.3.2, respectively. These inclusion and exclusion criteria are applicable to both Phase 2 and Phase 3 segments of the study.

There will be no prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions).

3.3.1. Inclusion Criteria (Part A)

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

1. Adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses (including CHF [including heart failure with preserved ejection fraction] and COPD), but should be medically stable as assessed by the following criteria:

- Absence of changes in medical therapy within 1 month due to treatment failure or toxicity
- Absence of medical events qualifying as SAEs within 1 month of the planned study injection on Day 1
- Absence of known, current, and life-limiting diagnoses, which could continue for the duration of the primary efficacy period (12 months from study injection on Day 1) and which, in the opinion of the investigator, would make completion of the protocol unlikely.

2. Body mass index from ≥ 18 kg/m^2 to ≤ 35 kg/m^2.
3. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
4. Able to comply with study requirements.

3.3.2. Exclusion Criteria (Part A)

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

1. Participation in another clinical research study where participant has received an investigational product (drug/biologic/device with the exception of investigational RSV products) within 6 months before the planned date of the Day 1 study injection. Current participation in another RSV investigational study is exclusionary.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
3. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease.
   Note: Human immunodeficiency virus (HIV) positive participants with CD4 count ≥ 350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy) as determined from participant's medical records, are permitted.

   Note: To clarify, participants with stable autoimmune diseases that do not require systemic immunosuppressants (per Exclusion Criterion #9) are permitted.
4. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or any components of the mRNA-1345 vaccine.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.

7. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
8. Received or plans to receive any nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 28 days before or after the Day 1 study injection. Nonstudy vaccination(s) should not be delayed.
9. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
10. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study injection or during the study.
11. Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥ 37.8°C (100.0°F) on the planned day of vaccine administration).
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. Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure > 160 mmHg at the Screening or baseline (Day 1) visit.
14. Known history of hypotension, or systolic blood pressure < 85 mmHg at the Screening or baseline (Day 1) visit.
15. Diastolic blood pressure > 90 mmHg at the Screening or baseline (Day 1) visit.
16. Known uncontrolled disorder of coagulation.
    Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation and under good control will NOT be excluded.
17. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
18. Donated ≥ 450 mL of blood products < 14 days prior to Screening.
19. Member of study personnel or is an immediate family member or household member of study personnel.

3.3.3. Inclusion and Exclusion Criteria Definitions (Part A)

For the purpose of study eligibility, the following definitions of symptomatic COPD, symptomatic CHF, exacerbation of COPD, and exacerbation of CHF will be used.

Term	Definition
Symptomatic COPD	Presence as defined by: Documented forced expiratory volume in 1 second/forced vital capacity < 0.7 after bronchodilator treatment **AND** Ongoing treatment with at least one of the following: an anticholinergic, a β2 agonist, inhaled glucocorticoids, or oral glucocorticoids < 10 mg of prednisone per day or equivalent for the above symptoms.
Exacerbation of COPD	An acute worsening of respiratory symptoms that results in additional therapy (GOLD 2020).
Symptomatic CHF (including heart failure with preserved ejection fraction)	Presence as defined by: At least 1 of the following signs or symptoms: shortness of breath with exercise, orthopnea, paroxysmal nocturnal dyspnea, dependent peripheral edema, or ascites **OR** A documented prior echocardiogram showing systolic and/or diastolic reduced ejection fraction **AND** Ongoing treatment with at least one of the following: a diuretic, an angiotensin-converting enzyme-inhibitor, β-blocker, or a cardiac glycoside.
Exacerbation of CHF	A clinical diagnosis based on at least one of the following symptoms: exertional dyspnea, fatigue, paroxysmal nocturnal dyspnea, orthopnea, cough, early satiety, weight gain, and increasing abdominal girth (Feiz et al 2015).

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

3.3.4. Participant Restrictions (Part A)

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

3.3.5. Screen Failures (Part A)

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

Participants meeting the Exclusion Criterion #11 (Section 3.3.2) of being acutely ill or febrile may be rescheduled within the relevant window periods and will retain their initially assigned participant number.

3.4. Study Treatment (Part A)

3.4.1. Investigational Product (Part A)

The term "IP" refers to both mRNA-1345 vaccine and placebo administered in this study.

The mRNA-1345 is an LNP dispersion of mRNA sequences encoding the RSV fusion glycoprotein stabilized in the prefusion conformation, formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000.

For the Phase 2 segment of the study, the mRNA-1345 vaccine will be provided as a sterile liquid for injection and will be a white to off-white dispersion, at a concentration of 0.4 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 8.6 mM sodium acetate at pH 7.5. For the Phase 3 segment of the study, mRNA-1345 vaccine will be provided as in the Phase 2 segment but at a concentration of 0.1 mg/mL in 20 mM Tris containing 87 mg/mL sucrose and 2.2 mM acetate at pH 7.5 (Table 7).

The placebo is 0.9% sodium chloride (normal saline) injection, which meets the criteria of the USP or equivalent as per local regulations (Table 7).

The IP (mRNA-1345 or placebo) will be administered as a 0.5-mL single IM injection on Day 1 to participants in both Phase 2 and Phase 3 segments of the study, according to the procedures specified in the mRNA-1345-P301 Pharmacy Manual.

Table 7: Investigational Product Administered (Part A)

Vaccination Group:	**Investigational Product**	**Placebo**
Intervention Name:	mRNA-1345	0.9% Normal Saline
Type:	Vaccine	Placebo
Dosage Level:	50 µg mRNA	N/A
Route of Administration:	IM injection	IM injection
Physical Description:	Sterile liquid for injection. White to off-white dispersion	A sterile, clear solution
Source:	Centrally provided by Sponsor	Hybrid – potentially centrally and locally
Packaging and Labeling:	mRNA-1345 will be provided in 2R glass vials. Each vial will be labeled as required per country requirement	Source dependent

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid; N/A = not applicable.

3.4.2. Dosing and Management of Investigational Product (Part A)

3.4.2.1. Method of Randomly Assigning Participants to Vaccination Groups (Part A)

The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pregenerated randomization schedules. Only the unblinded personnel (Section 3.4.2.8.1) will have controlled access to vaccination group assignments.

3.4.2.1.1. Stratification (Part A)

In both Phase 2 and Phase 3 segments of the study, assignment to vaccination groups will be stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent). The study will target enrollment of approximately 30% of participants 70 to 79 years of age and approximately 10% of participants ≥ 80 years of age (see Table 5 and Table 6). Risk will be defined based on the study participant's relevant past and current medical history. Participants will be categorized as at risk for LRTD if they have at least one of the following risk factors at Screening:

- CHF
- COPD

3.4.2.2. Administration of Investigational Product (Part A)

IP will be administered as a single IM injection into the deltoid muscle on Day 1. The injection will have a volume of 0.5 mL and contain 50 µg of mRNA-1345 or saline placebo. Preferably, vaccine should be administered into the nondominant arm.

The IP will be prepared for injection as a single 0.5-mL dose for each participant based on the randomization assignment, as detailed in the mRNA-1345-P301 Pharmacy Manual. Unblinded personnel who will not participate in any other aspect of the study will perform IP accountability, dose preparation, and IP administration. The investigator will designate unblinded medically qualified personnel (not involved in assessments of study endpoints) to administer the IP according to the procedures stipulated in this study protocol and the mRNA-1345-P301 Pharmacy Manual. Study-specific training will be provided.

At the visit when IP is administered, participants will be monitored for a minimum of 60 minutes after study injection. Assessments will include vital sign measurements and monitoring for local or systemic ARs (Table 20 and Table 21).

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

3.4.2.3. Delivery and Receipt (Part A)

The Sponsor or designee is responsible for the following:

- Supplying the IP

- Confirming the appropriate labeling of mRNA-1345 IP, so that it complies with local regulations.

The investigator is responsible for acknowledging the receipt of the IP by a designated study staff at the site, including the following:

- Confirming that the IP was received in good condition.
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate.
- Confirming whether the Sponsor has authorized the IP for use.
- Ensuring the appropriate dose level of mRNA-1345 is properly prepared using aseptic technique.

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1345-P301 Pharmacy Manual.

3.4.2.4. Packaging and Labeling (Part A)

The Sponsor will provide the investigator and study site with adequate quantities of mRNA-1345 vaccine. For the Phase 2 and Phase 3 segments of the study, the sterile vaccine product will be packaged in a 2R glass vial with 0.8-mL and 0.7-mL fill volumes, respectively. mRNA-1345 vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future participant identification purposes.

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

The Sponsor or designee will supply the 0.9% sodium chloride injection for use as both a placebo and a diluent to mRNA-1345. The 0.9% sodium chloride will be labeled with a study-specific label and Medical Identification number.

3.4.2.5. Storage (Part A)

The mRNA-1345 vaccine supplied for the Phase 2 segment of the study must be stored at -25°C to -15°C; for the Phase 3 segment, mRNA-1345-P301 is stored for 18 months at -25°C to -15°C that includes up to 180 days of storage at 2°C to 8°C and 48 hours at 8°C to 25°C. Vaccine must be stored in a secure area with limited access (unblinded personnel only) and protected from moisture and light until it is prepared for administration (Section 3.4.2.2). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid-response in case of freezer malfunction. In addition, vaccine accountability study staff (eg, the unblinded personnel) are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1345 vaccine that was not temperature controlled during shipment or during storage to the unblinded site monitor. Such mRNA-1345 vaccine will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

The 0.9% sodium chloride injection (normal saline) is stored according to the label.

3.4.2.6. Investigational Product Accountability (Part A)

It is the investigator's responsibility that the unblinded personnel maintain accurate records in an IP accountability log of receipt of all IP, inventory at the site, dispensing of mRNA-1345 and placebo, IP injections, and return to the Sponsor or alternative disposition of used/unused products.

An unblinded site monitor will review the inventory and accountability log during site visits and at the completion of the study. Additional details are found in the mRNA-1345-P301 Pharmacy Manual.

3.4.2.7. Handling and Disposal (Part A)

An unblinded site monitor will reconcile the IP during study conduct and at EOS for compliance. Once fully reconciled at the site at the EOS, the IP can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

IP may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be completed and sent to the Sponsor or designee.

3.4.2.8. Blinding (Part A)

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

The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end. The following study or site personnel are unblinded:

- Unblinded medically qualified study or site personnel will perform IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations or assessments of any study endpoints.
- Unblinded IP accountability monitors will ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned IAs (Section 3.7.6).
- An independent DSMB will review the interim data to safeguard the interests of clinical study participants and to help ensure the integrity of the study. The DSMB will review unblinded statistical outputs and IA results, provided by the independent unblinded statistician, and make recommendations to the Sponsor (Section 3.6.4.2). The DSMB functions will be defined in a separate charter.

3.4.2.8.1. Planned Unblinding (Part A)

If prespecified criteria for early efficacy are met by an IA or overall efficacy at the primary analysis, pre-identified Sponsor and contract research organization (CRO) team members responsible for the analysis and reporting will be unblinded to vaccination group assignments to prepare a CSR. To maintain an observer-blind design, investigators, study staff, participants, and Sponsor and CRO staff with oversight of study conduct will remain blinded to vaccination group allocation at least through the Month 24/EOS visit. Participants will be unblinded at or shortly after their Month 24/EOS visit. Unblinding may be performed via telephone, email, text message, or other electronic means based on participant preference. This individual unblinding is included to provide participants with timely information about their treatment allocation at the end of their study participation, as 2 licensed RSV vaccines are now available and may be indicated for some participants. All study participants will be followed for safety, efficacy, and immunogenicity endpoints through the end of the planned study period and results will be summarized in an end of study report.

A subset of participants at select US sites who consent to participate in the Part B substudy will be unblinded after giving consent and meeting initial eligibility criteria (ie, the participant meets all inclusion and exclusion criteria aside from Inclusion Criterion #5 [randomized to and subsequently received mRNA-1345 in Part A]). Participants will be consented and screened at the Month 24/EOS visit of Part A, which may be conducted up to 3 months (90 days) early. For participants who meet initial eligibility, vaccination group assignment will be unblinded to designated unblinded site staff. Participants who meet all eligibility criteria, including Inclusion Criterion #5, are eligible for Part B. Participants who are not eligible for Part B will complete study activities in Part A according to the Part A SoE (Table 20 and Table 21).

3.4.2.8.2. Unplanned Unblinding (Part A)

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill during the study, the study investigator may request that the blind be broken if knowledge of the administered vaccine will affect that participant's treatment options. In this situation or in the event of a medical emergency requiring identification of the IP administered to an individual participant, the investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblinding will be tracked via an audit trail in IRT and documented in the final study report.

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator must promptly contact the Sponsor (within 24 hours if possible) and document the circumstances on the appropriate forms.

3.4.3. Study Treatment Compliance (Part A)

All doses of IP will be administered at the study site under direct observation of unblinded medically qualified study personnel and appropriately recorded (date and time) in the electronic case report form (eCRF). Unblinded personnel will confirm that the participant has received the

entire dose of the IP. If a participant does not receive the IP, the reason for the missed dose will be recorded. Data will be reconciled with site accountability records to assess compliance.

3.4.4. Prior and Concomitant Therapy (Part A)

3.4.4.1. Prior Medications and Therapies (Part A)

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

3.4.4.2. Concomitant Medications and Therapies (Part A)

Study staff must question the participant regarding any medications taken and vaccinations received and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the study injection.
- Seasonal influenza vaccine administered for the current influenza season (as appropriate for a study site depending on whether it is in the Northern or Southern hemisphere).
- All concomitant medications and nonstudy vaccinations taken through 28 days after the study injection.
- Any concomitant medications and nonstudy vaccinations used to prevent or treat COVID-19, RSV disease, or any other infectious disease.
- Any concomitant medications relevant to or for the treatment of an AESI, SAE, or MAAE.
- 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 the study injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study staff during the post-injection study visits or via other participant interactions (eg, telephone, email, text message, or other electronic means).

3.4.4.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses (Part A)

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PP analysis (analysis sets are described in Section 3.7.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.
- A nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of the type of vaccine) administered during the period from

28 days before through 28 days after the study injection or an influenza vaccine during the period from 14 days before through 14 days after the study injection.

- Immunoglobulins and/or any blood products administered during the study period (except for treatment of COVID-19).
- Medications that suppress the immune system (except for treatment of COVID-19).

It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

All medication and interventions necessary for the appropriate care of the study participant, particularly to treat RSV, should be administered and appropriately documented along with the AE.

3.5. Delaying Or Discontinuing Investigational Product and Participant Withdrawal from the Study (Part A)

3.5.1. Criteria for Delay of Investigational Product Administration (Part A)

Vital signs, including oral body temperature, must be measured prior to IP administration. The following events constitute criteria for delay of study injection, and if any of these events occurs at the time scheduled for injection, the participant may be injected at a later date within the time window specified for Screening in Table 20 and Table 21.

- Acute moderate or severe infection with or without fever.
- Fever, defined as body temperature ≥ 37.8°C (100.0°F).
- In the opinion of the investigator, any clinically significant change in vital sign measurements or general condition from the Screening visit.
- Participant has received a nonstudy vaccine within protocol-specified Exclusion Criterion #8.

Participants with a minor illness without fever, as assessed by the investigator, can be administered the IP. Participants with a fever of 37.8°C (100.0°F) or higher and/or who meet any of these criteria for a delay in injection will be contacted within the time window acceptable for participation and reevaluated for eligibility.

3.5.2. Participant Withdrawal from the Study (Part A)

Participants who withdraw from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

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

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

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

- AE (specify)
- Death
- Lost to follow-up
- Physician decision (specify)
- Protocol violation (specify)
- SAE (specify)
- Solicited AR/ reactogenicity event (specify)
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study as result of an SAE or AE until resolution of the event, unless the participant declines further follow-up.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations) (Section 6.2.10).

3.5.3. Lost to Follow-up (Part A)

Participants will be considered lost to follow-up (LTFU) if they repeatedly fail to return for scheduled visits without stating an intention to withdraw consent and they cannot be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must attempt to regain contact with the participant. These contact attempts (eg, dates of telephone calls, contact logs, and registered letters) should be documented in the participant's medical record. A participant should not be considered LTFU until these efforts have been made.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

3.6. Study Assessments and Procedures (Part A)

Before undergoing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 6.2.6). Participants will undergo study procedures at the timepoints specified in the SoEs (Table 20 and Table 21).

A participant also can be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, symptoms of RSV-like illness, or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with the local regulations, investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoEs (Table 20 and Table 21). Adherence to the study design requirements is essential and required for study conduct.
- Visits (scheduled or unscheduled) may occur at the study site, mobile site, or other off-site location including the participant's home. Only the final eligibility/Day 1 visit is required to occur at the study site.
- The SoEs indicate the acceptable time windows around optimal timing of visits and safety contacts.
  - If a visit cannot be scheduled within the window and/or the participant misses the scheduled 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.
  - For a subset of participants at select US sites who consent to participate in the Part B substudy, the Month 24/EOS visit may be conducted up to 3 months (90 days) early; this is not considered a protocol deviation. If it is determined at the Part B Screening visit that a participant is not eligible for Part B, the participant will complete study activities in Part A according to the Part A SoE (Table 20 and Table 21).
  - Monthly safety contacts do not need to be performed in the months in which a scheduled visit is required (information that would be collected during a safety contact can be obtained during the scheduled visit). If a monthly safety contact cannot be made within the allowable timeframe according to the SoE, then site personnel should attempt to complete a safety contact at any other time within that calendar month.
  - If a participant misses a scheduled visit, a safety contact can be performed for that month but is not considered as a replacement for the scheduled visit.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should receive the study injection and/or continue participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Where permitted by local regulations, 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 SoEs (Table 20 and Table 21).
- Screening and Day 1 assessments may be performed on the same day or on different days. Additionally, the Screening visit may be performed over multiple visits if within the 14-day screening window.

3.6.1. Efficacy and Immunogenicity Assessments and Procedures (Part A)

3.6.1.1. Efficacy Assessments Related to RSV Infection (Part A)

Definitions of efficacy endpoints related to RSV infection are provided below. Note: The source of the clinical symptomology that supports the case definition can be participant reported and/or from a clinical assessment.

Endpoint	Definition
RSV-LRTD with 2 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.
RSV-LRTD with 3 or more symptoms	RT-PCR-confirmed RSV infection **PLUS** new or worsening of at least 3 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-LRTD.

Endpoint	Definition
RSV-ARD	RT-PCR-confirmed RSV infection **PLUS** an acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93%, or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-ARD.

3.6.1.2. Other Efficacy Assessments (Part A)

Definitions of efficacy endpoints not related to RSV infection are provided below. Note: The source of the clinical symptomology that supports the case definition can be participant reported and/or from a clinical assessment.

Endpoint	Definition
All-cause LRTD	New or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥ 37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause LRTD.
All-cause ARD	An acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of cough, stuffy nose, runny nose, sore throat, fever (≥ 37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause ARD.

3.6.1.3. Surveillance for RSV-Like Illness (Part A)

Starting from 14 days after the study injection and until EOS, participants will enter an active and passive surveillance period for respiratory disease. Participants will be given and trained to use an eDiary as described in Section 3.6.2.2 for weekly surveillance of respiratory symptoms and complete PRO questionnaires in case they report symptoms of RSV-like illness. Surveillance will include the following:

- Provision of a Participant ID Card, which provides details on study participation, site contact information, and a list of symptoms of respiratory disease. Participants should present this card to healthcare providers not affiliated with the study who encounter participants with symptoms of respiratory disease.
- The eDiary will provide weekly prompts (every 7 days) to elicit symptoms of RSV-like illness (new onset or worsening) and exposure to individuals with known RSV. The weekly eDiary prompt will inquire about the following:
  - Changes in health since the last time completing the weekly eDiary prompt or the last contact with the study staff.
  - Capture of any respiratory symptoms currently being experienced or experienced since the last time completing the weekly check-in as defined in Section 3.6.1.3.
  - Any contact with a healthcare provider that may indicate a MAAE.
- Participants are encouraged to respond to the eDiary as soon as possible if they have any symptom. If they do not have symptoms, they are encouraged to respond to the eDiary prompt at the end of the week from the trigger. Participants will be contacted by the study staff if they have missed reporting in the eDiary.
- If a participant reports RSV-like symptoms prior to the active and passive surveillance period (which starts on Day 15), the site staff should still arrange an illness visit; this is not considered a protocol deviation.
- If symptoms arise or worsen after the participant has completed the eDiary entry for a given week, the participant should contact the site to report symptoms of RSV-like illness.
- If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant, if possible, within 5 days after symptom onset or worsening for medical evaluation and nasopharyngeal swab collection. If the swab sample cannot be collected within 5 days after symptom onset or worsening, the sample may still be collected at the discretion of the site investigator if symptoms are still present (similarly, if symptoms are noted on Day 8 or Day 15, swab samples should still be collected even though this is within the 14 days after injection). Clinical information will be collected to evaluate the severity of the case. If the participant visited an external healthcare practitioner (HCP) because of the reported symptoms, site personnel are encouraged to obtain information from the HCP.
- All efforts must be made to collect a nasopharyngeal swab within 5 days of symptom onset for medical evaluation; however, if 5 days have elapsed since first symptom onset, swabs should still be collected as soon as possible, and this is not considered a protocol deviation.
- All participants who report new or worsening symptoms of RSV-like illness will receive eDiary prompts to complete the EQ-5D-5L (Section 3.6.9.1.2) and WPAI (Section 3.6.9.1.3) questionnaires.

Respiratory disease will be defined by a new onset or worsening (> 24 hours) of one or more of any of the following:

- Rhinorrhea

- Nasal congestion
- Pharyngitis (sore throat)
- Cough
- New or increased wheezing
- New or increased shortness of breath
- Tachypnea (≥ 20 breaths per minute)
- New or increased sputum production or a change in the volume or character of sputum
- Fever (≥ 37.8°C [100.0°F])
- Chills
- Hoarseness
- Sinus pain
- Pleuritic chest pain

"New onset" will require at least a 14-day period free of symptoms or with baseline symptoms, to differentiate an episode from any prior acute illness. "Worsening" will require > 24 hours of worsening of a chronic symptom (eg, worsening cough in a person with a chronic cough) or the occurrence of additional new or intensified respiratory symptoms. When any participant is determined to have a new or worsening respiratory disease, the participant will be invited to have an unscheduled visit and will be evaluated (and tested, if RSV is suspected). During this visit (unscheduled visit), which will occur within 5 days, if possible, of symptom onset or worsening, the following assessments will be performed:

- Review and confirmation of the history of respiratory disease, including approximate date of onset or worsening of respiratory disease and solicitation of each of the above-listed symptoms. Participants will also be asked about exposure to individuals with known RSV infection.
- Vital signs measurements, including resting respiratory rate and oxygen saturation (on room air or the participant's basal level of chronic supplemental oxygen use), which will be captured as numerical values.
- Ascertainment of HRQoL using the EQ-5D-5L questionnaire at the time of RSV symptom start and subsequent measurement times.
- Ascertainment of WPAI at 1 week and 2 weeks following start of RSV symptoms.
- Ascertainment of any visits to nonstudy HCPs, including a healthcare visit by the participant, a mobile/home visit by an HCP, or emergency room/urgent healthcare visit in response to the episode of respiratory disease. Site personnel are encouraged to attempt to obtain information from the HCPs.
- Ascertainment of hospital admission or prolongation of existing hospital stay in response to the episode of respiratory disease. Reporting procedures for SAEs should be followed (Section 3.6.3.10).

- Ascertainment of new concomitant medications (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from the respiratory disease.
- Collection of a specimen of upper respiratory secretions via nasopharyngeal swabs for detection of respiratory pathogens by reverse transcriptase polymerase chain reaction (RT-PCR) including coronavirus (229E, HKU1, NL63, OC43); human metapneumovirus; human rhinovirus/enterovirus; adenovirus; influenza A; influenza A H1; influenza A H1-2009; influenza A H3; influenza B; parainfluenza virus 1; parainfluenza virus 2; parainfluenza virus 3; parainfluenza virus 4; RSV-A; RSV-B; Chlamydia pneumoniae; Mycoplasma pneumoniae; and SARS-CoV-2. Data from specimens obtained using an RSV diagnostic test at a healthcare visit external to the study or mobile site may be accepted if the results are obtained using Food and Drug Administration (FDA)-approved kits or have laboratory developed tests within laboratories that are Clinical Laboratory Improvement Amendment (CLIA)-certified (or have similar regulatory certification for laboratories outside the US).

Note: RT-PCR testing for RSV and other pathogens by the study laboratory will be for the purposes of this protocol and not for clinical care. Conversely, local laboratory results, while informative to the clinician, will not be included as an endpoint for this study, unless the presence of RSV or other pathogen infection is diagnosed using an assay pertinent to state and federal regulations (eg, local CLIA-certified or a regulated laboratory). Data from specimens obtained using an RSV diagnostic test at a healthcare visit external to the study or mobile site may be accepted.

Participants will continue to complete the eDiary for ascertainment of respiratory symptom status. Subsequently, the study staff will contact the participants weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or through 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications. This follow-up will occur regardless of whether the participant had a positive test for RSV.

All clinical findings will be recorded in the eCRF.

3.6.1.4. Ancillary Supplies for Participant Use (Part A)

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions for recording solicited ARs in eDiaries (Section 3.6.2.2). Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

3.6.1.5. Immunogenicity Assessments (Part A)

Blood samples for immunogenicity assessments will be collected at the timepoints indicated in the SoEs (Table 20 and Table 21). Immunogenicity assessments will include the following:

- Serum binding Ab level to RSV
- Serum neutralizing Ab level to RSV-A and RSV-B

- Exploratory assays to characterize the immune responses to RSV or other respiratory viruses may be performed.

Serum will be tested using RSV-A and RSV-B neutralization assays as well as in a bead-based immunoassay specific to the RSV fusion glycoprotein. Immunogenicity analyses will be performed in a subset of participants. The selection of the subset and timepoints to be tested will be described in the SAP.

Testing will be performed in laboratories designated by the Sponsor using an appropriately validated clinical assay as per regulatory guidance.

3.6.2. Safety Assessments (Part A)

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 3.6.3.5) that occur during the 7 days following the study injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 3.6.2.2).
- Unsolicited AEs (Section 3.6.3.1) observed or reported during the 28 days following the study injection (ie, the day of injection and 27 subsequent days).
- AEs leading to discontinuation from study participation from Day 1 through EOS or withdrawal from the study.
- MAAEs from Day 1 through EOS or withdrawal from the study.
- AESIs from Day 1 through EOS or withdrawal from the study.
- SAEs from Day 1 through EOS or withdrawal from the study.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.

3.6.2.1. Safety Contact (Part A)

A safety contact is a telephone call or contact by electronic means made to the participant by medically qualified study staff. Medically qualified staff are those appropriately delegated individuals who are permitted to elicit verbal medical history from participants based on local regulations and local licensing requirements.

This contact communication will follow a script, which will facilitate the collection of relevant safety information. The participant will be interviewed, according to the script, about occurrence of unsolicited AEs (through 28 days post-vaccination), AESIs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations.

The timing of the safety contact and the relevant safety information collected is provided in the SoEs (Table 20 and Table 21).

All safety information described by the participant must be documented in source documents and not documented on the script used for the safety contact. All AEs, AESIs, MAAEs, SAEs, and AEs leading to study withdrawal must be recorded in the eCRF as specified in Section 3.6.3.6.

3.6.2.2. Use of Electronic Diaries (Part A)

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

Before enrollment on Day 1, the participant will be instructed or assisted with the download of the eDiary application on their personal smartphone or will be provided a Sponsor-provisioned device to record solicited ARs (Section 3.6.3.5) and to receive eDiary prompts for weekly follow-up of safety throughout the study and weekly surveillance for symptoms of RSV-like illness (Section 3.6.1.3).

On the day of study injection (Day 1), participants will be given eDiaries and trained to use them. Participants will record data into the eDiary starting approximately 60 minutes after injection under supervision of the study staff to ensure successful entry of assessments. The 60-minute assessment is an opportunity for study staff to train the participant. The study staff will perform any retraining as necessary. Study participants will continue to record in the eDiary solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of study injection and for 6 days following study injection.

The following local ARs will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (joint aches in several joints), nausea/vomiting, fever (oral temperature), and chills.

On the day of study injection (Day 1), participants will be instructed 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 to the side of injection.

Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.

All medications taken on the day of study injection and during the 28 days after the study injection (ie, the day of injection and 27 subsequent days) should be reported in the eDiary. Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on the day of study injection or for the 6 subsequent days.

Solicited local and systemic reactogenicity ARs, as defined in Section 3.6.3.5, will be collected on the day of study injection and during the 7 days after the study injection (ie, the day of

injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in an eDiary until it is no longer reported, not to exceed 28 days after the study injection. ARs recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or electronic means or at the following study visit, or during an unscheduled visit. (Table 20 and Table 21).

If eDiary prompts result in identification of relevant safety events according to the study period (or symptoms of respiratory disease; Section 3.6.1.3), a follow-up safety contact will be triggered to determine whether an unscheduled visit should be arranged.

If a participant does not respond to the weekly eDiary within 2 days after the scheduled timepoint, the study staff will follow-up directly with the participant via telephone call or other electronic means to confirm their health status and to remind the participant of the importance of maintaining weekly contact via the eDiary prompt.

3.6.2.3. Demographics/Medical History (Part A)

Demographic information relating to the participant's sex, age, and race will be recorded at the Screening visit on the appropriate eCRF page. Race and ethnicity data are collected to allow assessment of the extent to which results observed in study participants are generalizable to the target real-world population.

Medical history of each participant, including risk factors (eg, presence of CHF and/or COPD) for RSV disease as defined in Section 3.4.2.1.1, will be obtained by interviewing the participant or by reviewing the participant's medical records and recorded on the Medical History eCRF page. Significant findings that were present prior to the signature of the informed consent will also be included in the Medical History eCRF page. The participant's baseline frailty status will be assessed using the EFS (Rolfson et al 2006) and recorded on the appropriate eCRF page.

Study participants will also be asked to report history of receipt of seasonal influenza vaccine during the current influenza season (as appropriate for a site depending on whether it is located in the Northern or Southern hemisphere) as a concomitant medication; other prior and concomitant medications will be recorded as described (Section 3.4.4).

3.6.2.4. Physical Examination (Part A)

A full physical examination, including height and weight, will be performed at the Screening visit, and symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the discretion of the investigator. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Symptom-directed physical examinations may be performed at other timepoints at the discretion of the investigator.

On the day of study injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

Body mass index will be calculated at the Screening visit.

Significant new findings that begin or worsen after informed consent must be recorded on the AE eCRF page.

3.6.2.5. Vital Sign Measurements (Part A)

Vital signs will be measured at the timepoints indicated in the SoEs (Table 20 and Table 21). Vital signs measurements include systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation. The preferred route of temperature assessment is oral. The participant will be seated for at least 5 minutes before all measurements are taken. On the day of study injection, vital sign measurements will be collected once before the study injection and at least 60 minutes after the study injection (before participants are discharged from the study site). Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.

When applicable, vital sign measurements should be performed before blood collection.

Febrile participants on the day of study injection (fever is defined as a body temperature ≥ 37.8°C/100.0°F) may be rescheduled within the relevant window periods. Criteria for delay of study injection are provided in Section 3.5.1. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.6.2.6. Blood Sampling Volumes (Part A)

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. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Clarifications regarding sample volumes and practical details for the sites to follow are described in both the ICF and the Laboratory Reference Manual.

3.6.3. Safety Definitions and Procedures (Part A)

3.6.3.1. Adverse Event (Part A)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to IP or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

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

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the IP caused the AE (Section 3.6.3.5). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the IP and the AE.

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

3.6.3.2. Medically-Attended Adverse Events (Part A)

An MAAE is an AE that leads to an unscheduled visit to an HCP, where the participant seeks medical attention outside normal study procedures. This would include visits to a study or mobile site or at the home of the participant (where allowed by local regulations) for unscheduled assessments (eg, rash assessment) and visits to HCPs 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 on the AE page of the eCRF.

Visits due to surveillance for RSV that would normally have not resulted in consultation of an HCP should not be reported as a MAAE.

3.6.3.3. Adverse Events of Special Interest (Part A)

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required. Such events may require further investigation to characterize and understand them. Section 6.3 provides a full list of AESIs pertinent to this study. All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the electronic data capture system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI and the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox or the SAE Fax line (Section 3.6.3.10).

3.6.3.3.1. Anaphylaxis (Part A)

All suspected cases of anaphylaxis should be recorded as an AESI and reported as an SAE, based on criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 3.6.3.11. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs/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 hypersensitivity reaction with multi-organ 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.

3.6.3.3.2. Myocarditis/Pericarditis/Myopericarditis (Part A)

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 (Section 3.6.3.4). The CDC case definition is provided in Section 6.4 as guidance. These events will be reviewed by the independent Cardiac Event Adjudication Committee (CEAC; Section 3.6.4.3).

3.6.3.4. Serious Adverse Events (Part A)

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

Death
A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to IP.

Is life-threatening
An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Inpatient hospitalization or prolongation of existing hospitalization
In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency

ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.

Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Congenital anomaly or birth defect

Medically important event
Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

3.6.3.5. Solicited Adverse Reactions (Part A)

The term “reactogenicity” refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist. Participants will record such occurrences in an eDiary on the day of each IP injection and for the 6 days after the day of injection.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 8 modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after study injection, the participant will be prompted daily to capture solicited local or systemic AR in the eDiary until it is no longer reported, not to exceed 28 days after the study injection. ARs recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or other electronic means or at the following study visit, or during an unscheduled visit. All solicited ARs (local and systemic) will be considered causally related to IP injection.

Table 8: 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	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 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
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; 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 temperature)	< 38.0°C < 100.4°F	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	39.0°C – 40.0°C 102.1°F – 104.0°F	> 40.0°C > 104.0°F

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

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

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

3.6.3.6. Recording and Follow-up of an AE and/or SAE (Part A)

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor. Unsolicited AEs will be collected from the day of study injection through 28 days after the study injection.

Medically-attended AEs, AESIs, AEs leading to withdrawal from the study, and SAEs will be collected throughout the entire study duration, as specified in the SoEs (Table 20 and Table 21). Any AEs occurring before receipt of study injection will be analyzed separately from TEAEs.

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 3.5.3).

3.6.3.7. Time Period and Frequency for Collecting AE, AESI, and SAE Information (Part A)

All AESIs and SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 3.6.3.10. The investigator will submit any updated AESI or SAE data to the Sponsor within 24 hours of it being available.

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

3.6.3.8. Assessment of Intensity (Part A)

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 3.6.3.4), NOT when it is rated as severe.

The severity (or intensity) of an AE refers to the extent to which it affects the participant’s daily activities. Criteria for local and systemic ARs are presented in Section 3.6.3.5. The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definition of severity as follows:

- Mild: These events do not interfere with the participant’s daily activities.
- Moderate: These events cause some interference with the participant’s daily activities and require limited or no medical intervention.

- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

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

3.6.3.9. Assessment of Causality (Part A)

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

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

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

3.6.3.10. Reporting Adverse Events (Part A)

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

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes type of event, time of onset, investigator-specific assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant, including ongoing SAEs after study completion. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

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

Any AE that meets the AESI criteria (Section 3.6.3.3) or SAE criteria (Section 3.6.3.4) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the AESI or SAE). The investigator will assess whether there is a reasonable possibility that the IP caused the AESI or SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320 or applicable regulations outside of the US. The investigator is responsible for notifying the institutional review board (IRB)/independent ethics committee (IEC) directly.

If the eCRF is unavailable at the time of the SAE, the SAE Mailbox email address is below and the contact information to be used for SAE reporting is included in Section 6.5.

- SAE Mailbox: Drugsafety@modernatx.com

3.6.3.11. Regulatory Reporting Requirements for SAEs (Part A)

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/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

3.6.4. Monitoring Committees (Part A)

3.6.4.1. Internal Safety Team (Part A)

An IST will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the DSMB. The IST will comprise members not directly involved in the study.

3.6.4.2. Data and Safety Monitoring Board (Part A)

An independent DSMB will periodically review (through regular meetings) blinded and unblinded data, including both safety and cases of respiratory disease through the EOS. The DSMB will be composed of external independent subject matter experts and an unblinded statistician.

- The DSMB will review the IA results and make recommendations to the Sponsor.
- The DSMB will review the Day 29 safety data from the first 400 participants who receive the study injection in Phase 2 segment of the study; the DSMB review will trigger the enrollment in Phase 3 segment of the study.

The Sponsor may also request that the DSMB conduct ad hoc reviews of safety events from this study or other data, including new nonclinical or clinical information related to mRNA-1345 external to this study. The DSMB will review all available study data to make a recommendation in accordance with the DSMB charter.

The DSMB composition, its remit, and frequency of data review will be further defined in the DSMB charter and analysis plan.

3.6.4.3. Independent Cardiac Event Adjudication Committee (Part A)

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). The CDC Working Case Definitions are provided in Section 6.4 as guidance. Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then determine if additional action is needed. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

3.6.5. Management of Overdose (Part A)

As the study treatment is to be administered by an HCP, it is unlikely that an overdose will occur. Any dosing errors throughout the study will be reported as protocol deviations (Section 6.2.8). The HCP should be able to guide the participants for any additional treatment needed. The participant must be followed closely for safety.

3.6.6. Pharmacokinetics (Part A)

Pharmacokinetic parameters are not evaluated in this study.

3.6.7. Pharmacodynamics (Part A)

Pharmacodynamic parameters are not evaluated in this study.

3.6.8. Exploratory Assessments and Biomarkers (Part A)

Exploratory efficacy and immunogenicity objectives are listed in Section 3.1.3. Efficacy and immunogenicity assessments are described in Section 3.6.1.

Additional exploratory assessments related to PROs and medical resource utilization are described in Section 3.6.9.

3.6.9. Patient-Reported Outcomes and Medical Resource Utilization (Part A)

Objectives related to PROs and medical resource utilization to inform a separate economic analysis (if performed) are listed in Section 3.1.2.2 and Section 3.1.3. PROs and medical resource utilization associated with symptoms of RSV-like illness will be assessed at timepoints indicated in the SoEs (Table 20 and Table 21).

3.6.9.1. Patient-Reported Outcome Measures (Part A)

Patient-reported outcome measures will include the following questionnaires: EFS, EQ-5D-5L, and WPAI.

3.6.9.1.1. EFS (Part A)

The EFS (Rolfson et al 2006) is a brief, valid, and reliable tool for the assessment of frailty across 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. The participant's frailty status will be assessed at baseline, 12 months, and 24 months, and recorded on the appropriate eCRF page.

3.6.9.1.2. EQ-5D-5L (Part A)

The EQ-5D-5L consists of both the EQ-5D descriptive system and the EQ visual analogue scale.

For all participants, responses to the EQ-5D-5L will be collected using the eDiary at Day 1 and quarterly thereafter. For participants reporting symptoms of RSV-like illness, the EQ-5D-5L responses will be collected using the eDiary on the day that the symptoms start (up to 1 additional day), and at 4 days (± 1 day) and 14 days (± 1 day) after the start of the symptoms.

3.6.9.1.3. WPAI (Part A)

For all participants, the workplace productivity and activity impairment over the prior 7 days will be collected at the baseline assessment. For participants reporting symptoms of RSV-like illness, the WPAI over the previous 7 days will be collected using the eDiary at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms. The participant will be prompted to report productivity or activity impairment related to their respiratory illness symptoms. The list of the RSV symptoms that are part of their reporting of symptoms are the specific health problem to be considered.

3.6.9.2. Medical Resource Utilization (Part A)

Information on healthcare encounters, duration of hospital encounters, and new prescriptions for medications associated with any respiratory disease as well as cardiorespiratory hospitalizations and/or respiratory hospitalizations will be obtained from participant encounters during surveillance for RSV-like illness and scheduled and unscheduled study visits and safety contacts.

3.6.9.2.1. Hospitalization (Part A)

For hospital stays (new hospitalization or prolongation of existing hospitalization) resulting from symptoms of RSV including study endpoints (LRTD, ARD) or for AEs that qualify as SAEs due to hospitalization or prolongation of existing hospitalization, pertinent information will be collected via initial and updated reports to the safety database. Information to be collected for hospitalizations due to respiratory symptoms are described in Section 3.6.1.3. Regulatory reporting requirements must be observed for all SAEs (Section 3.6.3.11).

3.6.9.2.2. Outpatient Medical Resource Utilization (Part A)

For participants reporting MAAEs, outpatient medical resource utilization will be collected. Options provided are: outpatient/physician visit; emergency room/urgent care visit. Site personnel are recommended to obtain clinical information about the reported events from participant encounters with nonstudy HCPs.

3.7. Statistical Considerations (Part A)

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

3.7.1. Blinding and Responsibility for Analyses (Part A)

Blinding during the study will be conducted as described in Section 3.4.2.8. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for vaccination group assignment. Randomization will be implemented via an IRT.

Planned interim, primary, 12-month and final analyses are described in Section 3.7.6. Participant-level unblinding will be restricted to an independent unblinded statistician and as needed, a statistical programmer performing the IAs, who will have no other responsibilities associated with the study.

In addition to the routine study monitoring outlined in this protocol, an external DSMB will review interim data to safeguard the interests of clinical study participants and to enhance the integrity of the study. The DSMB will review treatment-level results of the IAs provided by the independent unblinded statistician. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IAs, if required, to act on the recommendations of the DSMB. The extent to which individuals are unblinded with respect to results of the planned IAs will be documented in the study DBP. Depending on the recommendation of the DSMB, the Sponsor may prepare a regulatory submission after an IA. In this case, pre-identified Sponsor members including the analysis and reporting team will be unblinded to treatment assignments and remain unblinded for the remainder of the study. Participants and investigators will remain blinded until the end of this study.

3.7.2. Statistical Hypotheses (Part A)

There are 2 primary efficacy objectives in this study, which will be tested in a hierarchical order, as stated in Section 3.7.6.2.

The first primary efficacy objective is to evaluate VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms. The corresponding null hypothesis is that the VE of mRNA-1345 as compared to a placebo to prevent the occurrence of protocol-defined RSV-LRTD with 2 or more symptoms is $\leq 20\%$ (ie, H^1_0: VE $\leq 20\%$). The VE is

defined as the percent of reduction in the hazards of the primary endpoint (mRNA-1345 vs. Placebo). Equivalently, the null hypothesis is: H^1_0: hazard ratio (HR) ≥ 0.8.

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1345 and placebo at a 1-sided 2.5% significance level.

The study will be considered to meet the first primary efficacy objective if the corresponding 2-sided (1-2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms rules out 20% at the time of analysis.

Once H^1_0 is rejected, the VE will be further evaluated for the second primary efficacy objective, evaluating VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms. The corresponding null hypothesis is that the VE of mRNA-1345 as compared to a placebo to prevent the occurrence of protocol-defined RSV-LRTD with 3 or more symptoms is ≤ 20% (ie, H^2_0: VE ≤ 20%). Equivalently, the null hypothesis is: H^2_0: HR ≥ 0.8.

The study will be considered to meet the second primary efficacy objective as long as the corresponding 2-sided (1-2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms rules out 20% at the time of analysis. Cases will be counted within the period of 14 days post-injection up to 12 months post-injection.

The primary analysis population for efficacy will be the PPE Set, defined in Section 3.7.4.

3.7.3. Sample Size Determination (Part A)

This Phase 2/3 study will plan to randomize approximately 37,000 participants (1:1 randomization ratio) to the mRNA-1345 or the placebo groups. Therefore, approximately 18,500 participants will be randomized to each group.

3.7.3.1. Power Calculation for Primary Efficacy Endpoint (Part A)

The sample size is driven by the total number of cases to demonstrate VE (mRNA-1345 vs. placebo) to prevent protocol-defined RSV-LRTD diseases.

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1345 and placebo, a total of 86 RSV-LRTD cases with 2 or more symptoms in the PPE Set will provide at least 90% power to demonstrate VE, ie, rejecting the null hypothesis H^1_0: VE ≤ 20%, with 2 IAs at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a 1-sided type I error rate of 2.5%.

The total number of cases pertains to the PPE Set within the period of 14 days post-injection up to 12 months post-injection. There are 2 planned IAs for this endpoint, which will be performed when at least 43 (50%) and at least 74 (85%) RSV-LRTD cases with 2 or more symptoms within the target total number of cases have been observed. Approximately 37,000 participants will be randomized with the following assumptions:

- The target VE against protocol-defined RSV-LRTD with 2 or more symptoms is 65%.
- An attack rate of 0.5% in the placebo arm for protocol-defined RSV-LRTD with 2 or more symptoms.

- Two IAs at approximately 50% and 85% of total target RSV-LRTD cases with 2 or more symptoms across the 2 vaccination groups in the PPE Set, respectively.
- A dropout rate ~10% (not evaluable for the PPE Set).
- Type I error rate will be adjusted using the Pocock boundary.

If the IAs are conducted exactly at 50% and 85% of total targeted cases, the nominal 1-sided type I error rate will be 1.55%, 1.18%, and 0.91% at IA1, IA2, and primary analysis, respectively.

In addition, the sample size, 37,000 participants and a total of 32 RSV-LRTD cases with 3 or more symptoms in the PPE Set, will provide approximately 89% power to demonstrate VE, ie, rejecting the null hypothesis H^2_0: VE ≤ 20%, with 2 IAs at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a 1-sided type I error rate of 2.5%.

The total number of cases pertains to the PPE Set within the period of 14 days post-injection up to 12 months post-injection. There are 2 planned IAs for this endpoint, which will be performed when approximately 16 (50%) and 28 (85%) RSV-LRTD cases with 3 or more symptoms within the target total number of cases have been observed. This sample size calculation is based on the following assumptions:

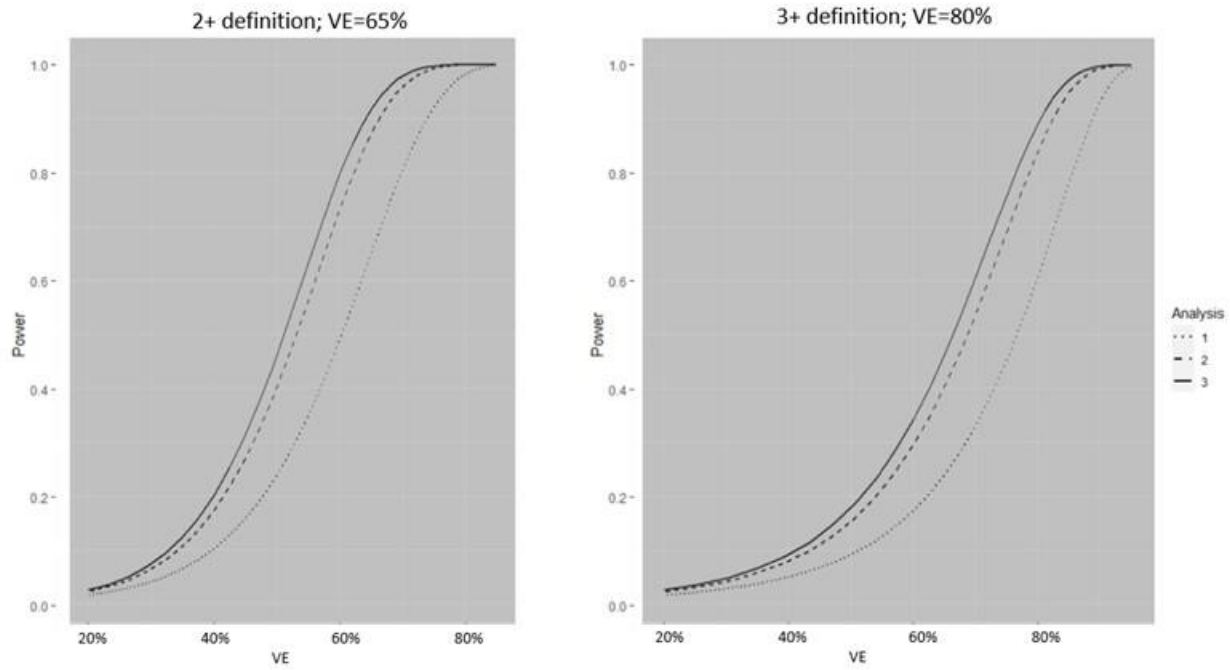
- The target VE against protocol-defined RSV-LRTD with 3 or more symptoms is 80%.
- An attack rate of 0.2% in the placebo arm for the protocol-defined RSV-LRTD with 3 or more symptoms.
- Two IAs at approximately 50% and 85% of total target RSV-LRTD cases with 3 or more symptoms across the 2 vaccination groups in the PPE Set, respectively.
- A dropout rate ~10% (not evaluable for the PPE Set).
- Type I error rate will be adjusted using the Pocock boundary.

It is expected the IA1 for both primary endpoints will be conducted at the same time, ie, IA1 will be conducted when at least 43 RT-PCR confirmed protocol-defined RSV-LRTD cases with 2 or more symptoms and at least 16 RT-PCR confirmed protocol-defined RSV-LRTD cases with 3 or more symptoms are observed in the PPE Set. Similarly, IA2 for both primary endpoints will be conducted at the same time.

Cases will be quantified (without unblinding) on an ongoing basis. If the targeted number of cases are not met in the original 37,000 participants, an extension of enrollment will be pursued. As the sample size recalculation will be performed without unblinding the study, no adjustment of the alpha for the primary analysis will be performed.

Figure 4 shows the power of the primary efficacy endpoints under the true VE at the 2 planned IAs and the primary efficacy analysis assuming a total of 86 RSV-LRTD cases with 2 or more symptoms and 32 RSV-LRTD cases with 3 or more symptoms, respectively.

Figure 4: Power of the Primary Efficacy Endpoints by Effect Size (Part A)



Abbreviations: 2+ definition = RT-PCR confirmed protocol-defined RSV-LRTD with 2 or more symptoms; 3+ definition = RT-PCR confirmed protocol-defined RSV-LRTD with 3 or more symptoms; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; RT-PCR = reverse transcriptase polymerase chain reaction VE = vaccine efficacy.

3.7.3.2. Power Calculation for the Key Secondary Efficacy Endpoints (Part A)

For the key secondary endpoints, with approximately 18,500 participants per group, Table 9 and Table 10 provide power of demonstrating VE based on an attack rate of 2.0% for a first episode of RSV-ARD and a rate of 0.2% for a first hospitalization associated with RSV-ARD or RSV-LRTD, respectively, under different scenarios of true VE and VE criteria at a 1-sided alpha level of 2.5% considering a ~10% ineligibility rate in the PPE Set. The study has at least 95% power to detect a VE = 50% against H^3_0: VE ≤ 20% to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection and approximately 90% power to detect a VE = 75% against H^4_0: VE ≤ 20% to prevent a first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

Table 9: Power of Demonstrating Vaccine Efficacy to Prevent a First Episode of RSV-ARD (Part A)

True VE	Placebo Attack Rate	VE to Prevent a First Episode of RSV-ARD	
		To Reject Null Hypothesis	Power
50%	2.0%	VE ≤ 20%	> 95%
55%			> 95%
60%			> 95%

Abbreviations: RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; VE = vaccine efficacy.

Table 10: Power of Demonstrating Vaccine Efficacy to Prevent a First Hospitalization Associated with RSV-ARD or RSV-LRTD (Part A)

True VE	Placebo Hospitalization Rate	VE to Prevent Hospitalizations Associated with RSV-ARD or RSV-LRTD	
		To Reject Null Hypothesis	Power
75%	0.2%	VE ≤ 20%	90%
80%			95%
85%			> 95%

Abbreviations: RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; VE = vaccine efficacy.

3.7.4. Analysis Populations (Part A)

Analysis populations for statistical analyses are Randomization Set, Full Analysis Set (FAS), modified Intent-to-Treat (mITT) Set, PP Immunogenicity (PPI) Set, PPE Set, Solicited Safety Set, and Safety Set, as shown in Table 11.

Table 11: Populations for Analyses (Part A)

Population	Description
Randomization Set	All participants who are randomized in the study, regardless of the participant's IP administration status. Participants will be included in the vaccination group to which they are randomized.
FAS	All randomized participants who receive any IP. Participants will be analyzed according to the vaccination group to which they are randomized.
mITT Set	All participants in the FAS who complete at least 1 visit or surveillance 14 days after the IP administration. The mITT Set will be the secondary population used for any immunogenicity analyses, disease incidence rate descriptions or efficacy estimates. Participants will be analyzed according to the vaccination group to which they are randomized. This set includes participants with major protocol violations.
PPI Set	A randomly selected subset of participants in the FAS who receive the assigned IP dose according to protocol, have RSV immunogenicity titer results at baseline (prior to the IP administration), at least 1 valid result after the IP administration at timepoint of interest, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined prior to database lock and unblinding. The PPI Set will be the primary population used for immunogenicity analyses, including exploration of immunologic correlates of risk. Participants will be analyzed according to the vaccination group to which they are randomized.

Population	Description
PPE Set	All participants in the mITT Set who receive the assigned IP dose according to protocol, complete at least 1 visit or surveillance contact 14 days after the IP administration, and have no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding. The PPE Set will be the primary population for efficacy analyses, for the description of RSV disease rates among placebo recipients, and for the exploratory estimation of vaccine efficacy against health outcomes associated with various RSV disease endpoints. Participants will be analyzed according to the vaccination group to which they are randomized.
Solicited Safety Set	All randomized participants who receive any IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the IP that they actually receive.
Safety Set	All randomized participants who receive any IP. The Safety Set will be used for all analyses of safety. Participants will be included in the vaccination group corresponding to the IP that they actually receive.

Abbreviations: AR = adverse reaction; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PPE = per-protocol efficacy; PPI = per-protocol immunogenicity; RSV = respiratory syncytial virus.

3.7.5. Statistical Analyses (Part A)

This section provides a summary of the planned statistical analyses of the primary, key secondary, and other secondary endpoints.

The overall type I error rate for the primary endpoint at the IAs and the primary analysis is strictly controlled at 2.5% (1-sided) based on the Lan-DeMets spending function (see Section 3.7.6 for details). The primary efficacy results that will be considered statistically significant after consideration of the strategy for controlling the type I error as described in Section 3.7.6.2. Statistical significance of the primary efficacy endpoints can be achieved at either of the IAs or at the primary analysis.

A sequential/hierarchical testing procedure will be used to control type I error rate over the primary efficacy endpoints, key secondary efficacy endpoints, and other secondary efficacy endpoints. Key secondary efficacy endpoints and selected secondary efficacy endpoints will only be tested at the planned analysis at 12 months or final analysis, whichever is applicable, when both primary efficacy endpoints achieve statistical significance. In that case, see Section 3.7.6.2. for the multiplicity adjustments among the key secondary and other selected secondary efficacy endpoints.

No formal multiplicity adjustments will be employed for safety endpoints.

All analyses will be performed by vaccination group, unless specified otherwise. For categorical variables, frequencies and percentages will be presented. Continuous variables will be

summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

3.7.5.1. Efficacy Analyses (Part A)

Efficacy analyses will be performed using the mITT and PPE Sets, and participants will be included in the vaccination group to which they are randomized. The primary analysis population for efficacy will be the PPE Set.

Table 12 summarizes the analysis approach for primary and key secondary endpoints.

Table 12: Statistical Analysis Methods for Primary and Key Secondary Efficacy Endpoints (Part A)

Endpoint	Statistical Analysis Method
• Primary endpoint 1: VE of mRNA-1345 to prevent the first occurrence of protocol-defined RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection • Primary endpoint 2: VE of mRNA-1345 to prevent the first occurrence of protocol-defined RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection	• Primary analysis: VE will be estimated with 1 − HR (mRNA-1345 vs placebo) using a stratified Cox proportional hazard model based on the PPE Set. • Analysis using the same model based on the mITT Set. • Subgroup analysis of the primary efficacy endpoint will be performed to assess consistency of VE in different age groups. • Supportive analysis using exact method based on incidence rate. • Supportive analysis of VE to be estimated with 1- the ratio of incidence rates, using the Farrington and Manning's score method based on the PPE Set. • Additional descriptive analyses.
• Key secondary endpoints	Similar analysis method as for the primary endpoint analysis. For each endpoint: • VE will be estimated with 1 − HR (mRNA-1345 vs placebo) using a stratified Cox proportional hazard model based on the PPE Set. • Analysis using the same model based on the mITT Set. • Subgroup analysis of the key secondary efficacy endpoints will be performed to assess consistency of VE in different age groups. • Supportive analysis using exact method based on incidence rate. • Supportive analysis of VE to be estimated with 1- the ratio of incidence rates, using the Farrington and Manning's score method based on the PPE Set. • Additional descriptive analyses.

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; PPE = per-protocol efficacy; RSV – LRTD = respiratory syncytial virus-associated lower respiratory tract disease; VE = vaccine efficacy.

3.7.5.1.1. Analysis of Primary Efficacy Endpoints (Part A)

To assess the primary efficacy endpoint of VE of mRNA-1345 in preventing the first occurrence of protocol-defined RSV-LRTD with 2 or more (or 3 or more) symptoms within the period of 14 days post-injection up to 12 months post-injection, Cox proportional hazards regression model based on PPE Set will be used to estimate HR. The VE, ie, 1-HR (mRNA-1345 vs. placebo) will be estimated with a 2-sided (1-2 × adjusted alpha) × 100% CI and a 1-sided p-value for testing H^1_0: VE ≤ 20% or H^2_0: VE ≤ 20%.

The VE is defined as percent of reduction in the hazards of the primary endpoint (mRNA-1345 vs. placebo) and will be estimated using 1-HR estimand. A stratified Cox proportional hazard model with vaccination group as a fixed effect and stratification factors for randomization as covariates will be used based on the PPE Set to estimate the HR (mRNA-1345 vs. placebo). The Efron's method will be used to handle ties.

For the primary efficacy endpoints, participants without RT-PCR confirmed protocol-defined RSV-LRTD will be censored at the last study assessment date. Potential intercurrent events may include: 1) early discontinuation or death unrelated to RSV-LRTD; and 2) early RSV-LRTD up to 14 days after study dose.

The study will be considered to meet the primary efficacy objective as long as the corresponding 2-sided (1-2 × adjusted alpha) × 100% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more (or 3 or more) symptoms rules out 20% at the time of analysis. The 1-sided adjusted alpha at the IAs and primary analysis will be 1.55%, 1.18%, and 0.91% at IA1, IA2, and primary analysis, respectively, with overall 1-sided alpha for the primary endpoint = 2.5% (see Section 3.7.6 for details).

Analyses of the primary endpoint will be performed based on the mITT Set using the same methods described above.

Subgroup analysis of the primary efficacy endpoint will be performed to assess consistency of VE as described in Section 3.7.5.5.

To support the primary analysis, VE will also be estimated by 1 minus the ratio of incidence rates adjusting for person-time, and the 95% CI of VE will be computed using the exact method, conditional upon the total number of cases adjusting for person-time.

Farrington and Manning's score method (Farrington and Manning 1990) based on PPE Set will also be applied as a supportive analysis to estimate VE with a 2-sided Farrington and Manning score-based 95% CI. The VE is estimated by 1 minus the ratio of incidence rates (mRNA-1345 versus placebo).

Kaplan-Meier curves will be used to plot the estimated cumulative incidences over time by vaccination group. Cases of protocol-defined RSV-LRTD for both primary endpoints will be counted within the period of 14 days after injection up to 12 months post-injection, and participants without a case identified up to 12 months post-injection will be censored at 12 months. Descriptive statistics for the mRNA-1345 and placebo groups will also be produced.

Full details will be documented in the SAP.

3.7.5.1.2. Analysis of Key Secondary and Secondary Efficacy Endpoints (Part A)

Analyses of key secondary efficacy endpoints are summarized in Table 2.

Negative binomial regression will be used for estimating VE of mRNA-1345 to prevent all-cause LRTD and all-cause hospitalization cases which could occur multiple times during the selected observation period.

An analysis of covariance model with the vaccination group as explanatory variable, adjusting for the stratification factor at randomization, baseline value if applicable, will be used to assess the treatment effect for the total frailty score from baseline to 12 months and 24 months post-injection.

Other secondary efficacy endpoints will be analyzed in a similar way as the primary analysis for the primary efficacy endpoints.

More details can be found in the SAP.

3.7.5.2. Safety Analyses (Part A)

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group.

3.7.5.2.1. Adverse Events (Part A)

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, vital signs, and physical examination findings.

Unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used in this study for the collection and severity grading of solicited ARs.

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

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, AESIs, severe AEs, and AEs leading to discontinuation from the study will be summarized. Number of events of unsolicited AEs, SAEs, MAAEs, and AESIs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 13 summarizes analysis strategy for safety parameters. Further details will be described in the SAP.

Table 13: Analysis Strategy for Safety Parameters (Part A)

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any AESI	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically-attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by system organ class and preferred term coded by MedDRA.

3.7.5.2.2. Baseline Descriptive Statistics (Part A)

Demographic variables (eg, age, height, weight, and body mass index) and baseline characteristics will be summarized by vaccination group using descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

3.7.5.3. Immunogenicity Analyses (Part A)

The secondary immunogenicity endpoints will be analyzed using the PPI Set, by vaccination group, unless otherwise specified.

Data from immunogenicity assays will be summarized for each vaccination group using SRRs and GM with 95% CIs, for each timepoint for which an assessment is performed.

For the immunogenicity endpoints, GM of specific Ab titers with corresponding 95% CI at each timepoint and GMFR of specific Ab titers with corresponding 95% CI at each postbaseline timepoint over preinjection baseline at Day 1 will be provided by vaccination group. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For summaries of geometric mean titers/concentrations (GMTs/GMCs), Ab titers/concentrations 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, unless otherwise specified.

The SRR of RSV nAbs is defined as the proportion of participants with post-vaccination titers ≥ 4 × LLOQ if baseline is < LLOQ or a ≥ 4-fold increase from baseline if baseline is ≥ LLOQ.

Proportion of participants with seroresponse will be provided with 2-sided 95% CI using the Clopper-Pearson method by postbaseline timepoint.

Further details, including the participant sampling plan, will be described in the SAP.

3.7.5.4. Exploratory Analyses (Part A)

Exploratory endpoints evaluating VE will be assessed by similar analysis methods as used for the analysis of the primary efficacy endpoint.

Analyses of the remaining efficacy and immunogenicity exploratory endpoints will be described in the SAP.

3.7.5.5. Subgroup Analyses (Part A)

If sufficient case numbers of the primary and key secondary endpoints in a subgroup (ie, age or risk factors for LRTD) are available, subgroup analysis may be performed.

3.7.6. Planned Analyses (Part A)

3.7.6.1. Interim Analyses (Part A)

Two IAs, 1 primary analysis, 1 potential analysis at 12 months, and 1 final analysis are planned.

1. The first IA will be performed when approximately 50% of the planned cases (at least 43 RSV-LRTD cases with 2 or more symptoms and 16 RSV-LRTD cases with 3 or more symptoms) have occurred.
2. The second IA will be performed when approximately 85% of the planned cases (at least 74 RSV-LRTD cases with 2 or more symptoms and 28 RSV-LRTD cases with 3 or more symptoms) have occurred.
3. The primary analysis will be performed when approximately 86 RSV-LRTD cases with 2 or more symptoms and 32 RSV-LRTD cases with 3 or more symptoms have occurred.
4. The analysis at 12 months may be conducted for some secondary and exploratory endpoints, as appropriate.
5. The final analysis will be performed when all participants have completed Month 24 follow-up.

There are 2 planned IAs at 50% and 85% of total target cases across the 2 groups for the 2 null hypotheses to be tested to support the primary objectives. The intent of the IAs is for early detection of reliable evidence that VE of mRNA-1345 is above 20%. The Lan-DeMets Pocock approximation spending function is used to preserve the (1-sided) 2.5% type I error rate over the IAs and the primary analysis (when the target number of cases have been observed), relative to the hypothesis:

H^1_0: VE $\leq$ 0.2 (equivalently, HR $\geq$ 0.8) and H^2_0: VE $\leq$ 0.2 (equivalently, HR $\geq$ 0.8).

If efficacy is demonstrated for a primary endpoint at an IA, the subsequent IA or primary analysis for this primary endpoint will be considered supportive in nature. The DSMB will review the IA results and make recommendations to the Sponsor in terms of study results

reporting and unblinding based on the boundaries of early efficacy as described in this section, safety data, and data external to this study.

IA1 will occur when approximately 50% of the total cases have been observed (across both vaccination groups) for both primary endpoints in the PPE Set. The study will be considered positive to meet the first primary objective at IA1 if the lower bound of 2-sided 96.9% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms rules out 20%. Once the first primary objective is met at IA1, the study will be considered positive to meet the second primary objective at IA1 if the lower bound of 2-sided 96.9% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms rules out 20%, provided that IA1 is conducted exactly at 50% information fraction for both primary endpoints.

If neither H^1_0 nor H^2_0 is rejected at IA1, IA2 will occur when approximately 85% of the total cases have been observed (across both vaccination groups) for both primary endpoints in the PPE Set. The study will be considered positive to meet the first primary objective at IA2 if the lower bound of 2-sided 97.64% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 2 or more symptoms rules out 20% at IA2. The study will be considered positive to meet the second primary objective at IA2 if H^1_0 is rejected and the lower bound of 2-sided 97.64% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms rules out 20% at IA2, provided that IA1 and IA2 are conducted exactly at 50% and 85% information fraction for both primary endpoints, respectively.

If H^1_0 is rejected and H^2_0 is not rejected at IA1, IA2 will occur when approximately 85% of the total cases have been observed for the second primary endpoint in the PPE Set. The study will be considered positive to meet the second primary objective at IA2 if the lower bound of 2-sided 97.64% CI of VE of mRNA-1345 as compared to a placebo to prevent protocol-defined RSV-LRTD with 3 or more symptoms rules out 20% at IA2, provided that IA1 and IA2 are conducted exactly at 50% and 85% information fraction, respectively.

Cases will be quantified (without unblinding) on an ongoing basis. If the targeted number of cases are not met in the original 37,000 participants, an extension of enrollment will be pursued. As the sample size recalculation will be performed without unblinding the study, no adjustment of the alpha for the primary analysis will be performed.

The IAs will be presented to the DSMB. Details of the planned analysis and communication process will be provided in the SAP and the DSMB charter.

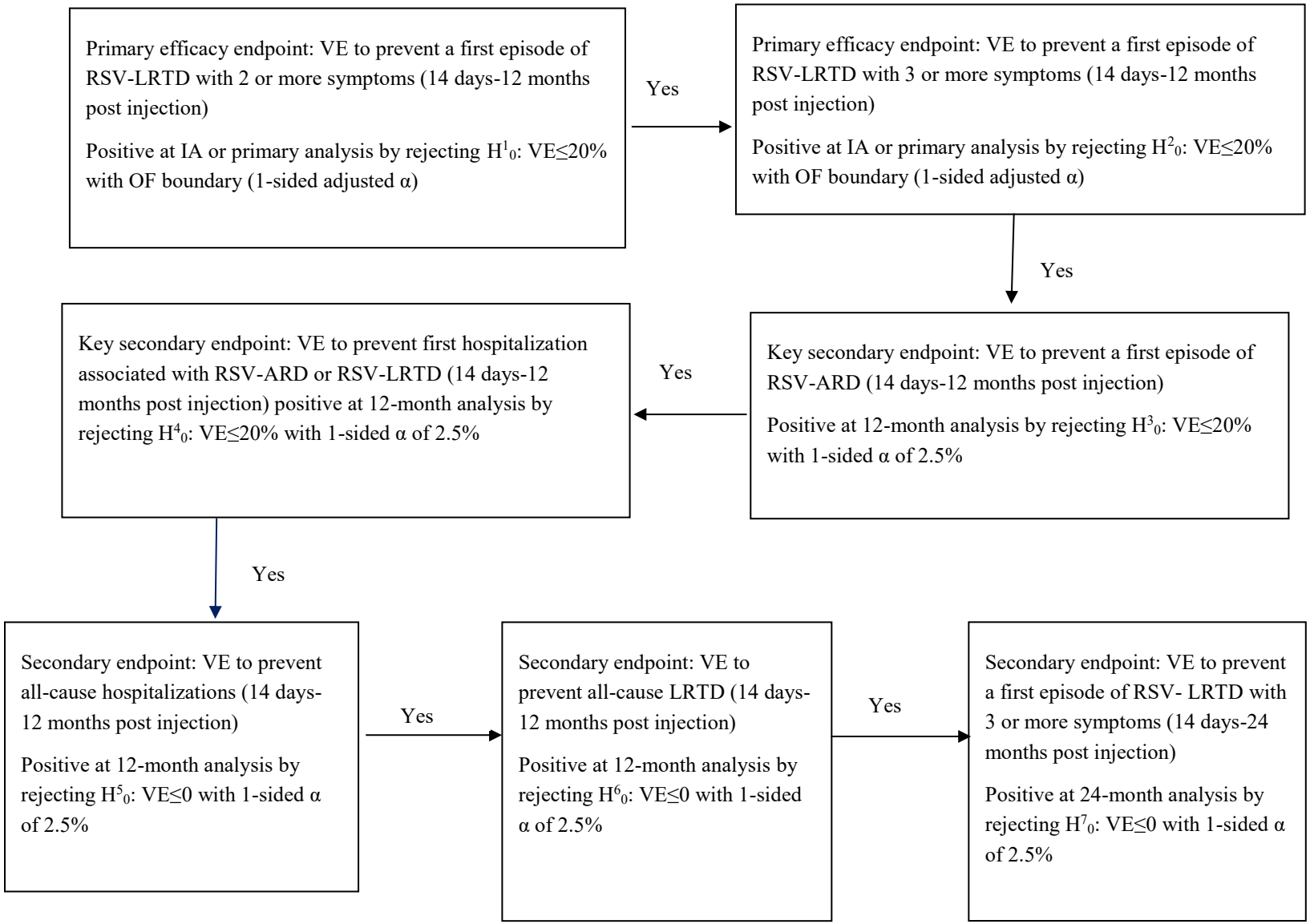
3.7.6.2. Multiplicity (Part A)

The overall type I error rate of this study is strictly controlled at 2.5% (1-sided). The overall type I error rate for the primary efficacy endpoints at the IAs and the primary analysis is strictly controlled at 2.5% (1-sided) based on the Lan-DeMets Pocock approximation spending function. A hierarchical testing strategy will be used to test the primary, key secondary and 3 selected secondary endpoints (Figure 5).

Statistical significance of the primary efficacy endpoints can be achieved at either of the IAs or at the primary analysis with a hierarchical order of RSV-LRTD with 2 or more symptoms followed by RSV-LRTD with 3 or more symptoms. If the primary efficacy endpoints achieve statistical

significance at either one of the interim analyses or at the primary analysis, a fixed-sequence hierarchical testing with a predefined order as shown in Figure 5 will be used to test the key secondary endpoints and 3 selected secondary efficacy endpoints at the time of planned 12-month analysis or final analysis, whichever is applicable. Sequential testing of the key secondary and selected secondary endpoints will be performed at 1-sided type I error rate of 2.5%. The detailed multiplicity adjustments among the secondary efficacy endpoints will be specified in the SAP.

Figure 5: Testing Sequence of the Primary, Key Secondary, and Secondary Endpoints (Part A)



4. PART B SUBSTUDY (SELECT US SITES ONLY)

4.1. Objectives and Endpoints (Part B Substudy)

4.1.1. Primary Objectives and Endpoints (Part B Substudy)

The primary objectives and endpoints for the Part B substudy are given in Table 14.

Table 14: Primary Objectives and Endpoints (Part B Substudy)

Primary Safety Objective	Primary Safety Endpoints
• To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose.	• Numbers and percentages of participants with: – Solicited local and systemic ARs through 7 days post-BD injection. – Unsolicited AEs through 28 days post-BD injection. – MAAEs, AESIs, SAEs, and AEs leading to withdrawal BD Day 181/EOS.
Coprimary Immunogenicity Objectives	**Coprimary Immunogenicity Endpoints**
• To demonstrate noninferiority of the serum RSV-A nAb response of a BD of mRNA-1345 compared with a primary dose.	• GMT of serum RSV-A nAb at BD Day 29. • GMR of serum RSV-A nAb GMT at BD Day 29 over serum RSV-A nAb GMT at Primary Dose Day 29.
• To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.	• GMT of serum RSV-B nAb at BD Day 29. • GMR of serum RSV-B nAb GMT at BD Day 29 over serum RSV-B nAb GMT at Primary Dose Day 29.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BD = booster dose; EOS = end of study; GMR = geometric mean ratio; GMT = geometric mean titer; MAAE = medically-attended adverse event; nAb = neutralizing antibody; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SAE = serious adverse event.

4.1.2. Secondary Objectives and Endpoints (Part B Substudy)

The secondary objectives and endpoints for the Part B substudy are given in Table 15.

Table 15: Secondary Objectives and Endpoints (Part B Substudy)

Secondary Immunogenicity Objectives	Secondary Immunogenicity Endpoints
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 administered 24 months after the primary dose of mRNA-1345 based on seroresponse.	• SRR difference between serum RSV-A nAb at BD Day 29 and serum RSV-A nAb at Primary Dose Day 29. • SRR difference between serum RSV-B nAb at BD Day 29 and serum RSV-B nAb at Primary Dose Day 29.

Secondary Immunogenicity Objectives	Secondary Immunogenicity Endpoints
• To evaluate the immune response to RSV-A and RSV-B of a BD of mRNA-1345 up to 6 months post-BD injection.	• GMT of serum RSV-A nAb at BD Day 1 and BD Day 181/EOS. • GMFR of serum RSV-A nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • GMT of serum RSV-B nAb at BD Day 1 and BD Day 181/EOS. • GMFR of serum RSV-B nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • SRR of serum RSV-A nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS. • SRR of serum RSV-B nAb from pre-Primary Dose (baseline) at BD Day 1, BD Day 29, and BD Day 181/EOS.

Abbreviations: BD = booster dose; EOS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; nAb = neutralizing antibody; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate.

4.1.3. Exploratory Objectives and Endpoints (Part B Substudy)

The exploratory objectives and endpoints for the Part B substudy are given in Table 16.

Table 16: Exploratory Objectives and Endpoints (Part B Substudy)

Exploratory Immunogenicity Objectives	Exploratory Immunogenicity Endpoints
• To evaluate the long-term immune response to RSV-A and RSV-B among Part B participants who received placebo.	• GMT of serum RSV-A nAb and RSV-B nAb at prespecified study timepoints. • GMFR of serum RSV-A and RSV-B relative to pre-Primary Dose (baseline) at prespecified study timepoints. • SRR of serum RSV-A nAb at prespecified study timepoints. • SRR of serum RSV-B nAb at prespecified study timepoints. • Proportion of participants with ≥ 2-fold increase in serum RSV-A and RSV-B nAb levels from pre-Primary Dose (baseline) at prespecified study timepoints.
• To evaluate occurrence of RSV disease after a BD of mRNA-1345.	• Number and incidence of cases of the following: – RSV-LRTD with 2 or more symptoms – RSV-LRTD with 3 or more symptoms – RSV-ARD – Hospitalization From 14 days post-BD injection to BD Day 181/EOS.

Abbreviations: BD = booster dose; EOS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; nAb = neutralizing antibody; RSV = respiratory syncytial virus; RSV-A = respiratory syncytial virus-A; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-B = respiratory syncytial virus-B; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SRR = seroresponse rate.

4.2. STUDY DESIGN (Part B Substudy)

4.2.1. General Design (Part B Substudy)

This is a Phase 3, randomized, observer-blinded, placebo-controlled substudy to evaluate the safety, tolerability, and immunogenicity of revaccination with a BD of 50 µg of mRNA-1345 in participants who were randomized to and were subsequently vaccinated with the mRNA-1345 study injection in Part A. For the purposes of this substudy, the terms revaccination and booster are used interchangeably. The Part B substudy will be conducted at select US sites only.

Approximately 1500 participants will be randomly assigned in a 2:1 randomization ratio to receive a single BD injection of either 50 µg of mRNA-1345 or placebo.

Participants will be consented and screened for Part B at the Month 24/EOS visit for Part A, which may be conducted up to 3 months (90 days) early. Potential participants must sign the Part B ICF and undergo screening activities to confirm initial eligibility (ie, the participant meets all inclusion and exclusion criteria aside from Inclusion Criterion #5 [randomized to and subsequently received mRNA-1345 in Part A]). For participants who meet initial eligibility, vaccination group assignment will be unblinded to designated unblinded site staff. Participants who meet all eligibility criteria, including Inclusion Criterion #5, are eligible for the Part B substudy. Participants who are not eligible for Part B will complete study activities in Part A according to the Part A SoE (Table 20 and Table 21).

Part B study duration will be approximately 6 months for each participant. All participants will complete up to 4 scheduled in-person visits, including Screening/BD Day 1, BD Day 29, and BD Day 181/EOS. All participants will have a safety contact (via telephone, email, text message, or other electronic means) on BD Day 8, BD Day 60, and every 60 days thereafter. The SoE is given in Table 22 and the study schema is given in Figure 3. Details about handling of missed or delayed visits and other participant encounters are provided in Section 4.6.

Participants will be given and trained to use an eDiary on the day of study injection (BD Day 1) to report solicited ARs and all other AEs for 7 days after the study injection.

Safety contacts (Section 4.6.2.1) will be performed throughout the substudy and are intended to capture SAEs, MAAEs, hospitalizations, and outpatient treatments related to or for the treatment of the MAAEs or SAEs, AESIs, AEs leading to withdrawal, concomitant medications associated with these events, and/or receipt of nonstudy vaccinations.

All participants will be assessed for immunogenicity endpoints at BD Day 1, BD Day 29, and BD Day 181/EOS.

Active and passive surveillance will be conducted for RSV-like illness and exposure to individuals with known RSV, also using the eDiary, starting from 14 days after the study injection until BD Day 181/EOS. See Section 4.6.5.2 for symptoms of respiratory disease that will be surveyed and for details about eDiary prompts and unscheduled visits.

All participants will be assessed for safety, immunogenicity, and RSV surveillance/infection endpoints up to 6 months after the BD study injection. See the SoE (Table 22) for the frequency and timing of safety, immunogenicity, and RSV surveillance assessments.

Participants will be considered to have completed the Part B substudy if they complete the final visit at BD Day 181, 6 months after receiving the BD study injection. The EOS for Part B is defined as completion of the last visit of the last participant in the substudy or last scheduled procedure as shown in the SoE (Table 22) for the last participant in the substudy.

Except for appropriately delegated unblinded pharmacists, vaccine administrators, clinical study managers, and monitors, all personnel involved in the conduct of the substudy will remain blinded to individual vaccination assignment until planned study unblinding (details can be found in Section 4.4.2.8.1.

Safety will be closely monitored and reviewed by the ongoing IST.

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

4.2.2. Scientific Rationale for Study Design (Part B Substudy)

This substudy is designed to evaluate the safety, tolerability, and immunogenicity of revaccination with a BD of 50 µg of mRNA-1345 in participants who were randomized to and were subsequently vaccinated with the mRNA-1345 study injection in Part A. Demonstration that a BD of 50 µg of mRNA-1345 has an acceptable safety profile and induces immune responses that are noninferior to those induced by a primary dose of 50 µg of mRNA-1345 in this target population may support the use of 50 µg of mRNA-1345 for periodic boosting, if necessary.

4.2.3. Choice of Dose and Control Product (Part B Substudy)

The 50-µg dose of mRNA-1345 and the 0.9% sodium chloride (normal saline) placebo control were selected for this substudy to allow for noninferiority comparisons to Part A and were based on positive safety and efficacy results from a prespecified IA of the current study (mRNA-1345-P301; data cutoff 30 Nov 2022) as described in Section 2.2.2.

4.2.4. End of Study Definition (Part B Substudy)

Participants will be considered to have completed the Part B substudy if they complete the final visit at BD Day 181, 6 months after receiving the BD study injection.

The EOS of Part B is defined as completion of the last visit of the last participant in the substudy or last scheduled procedure as shown in the SoE (Table 22) for the last participant in the substudy.

4.3. Study Population (Part B Substudy)

The study population will consist of adults ≥ 60 years of age with or without underlying medical conditions who were randomized to and were subsequently vaccinated with a primary dose of mRNA-1345 in Part A.

There will be no prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions). No exceptions will be made for participants with protocol deviations to the Part A inclusion/exclusion criteria.

4.3.1. Inclusion Criteria (Part B Substudy)

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

1. Adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical diagnoses (including CHF [including heart failure with preserved ejection fraction] and COPD) but should be medically stable as assessed by the following criteria:
   - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity.
   - Absence of medical events qualifying as SAEs within 1 month of the planned study injection on BD Day 1.
   - Absence of known, current, and life-limiting diagnoses, which could continue for 6 months from study injection on BD Day 1, and which, in the opinion of the investigator, would make completion of the protocol unlikely.
2. Body mass index from ≥ 18 kg/m^2 to ≤ 35 kg/m^2.
3. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment.
4. Able to comply with study requirements.
5. Randomized to and were subsequently vaccinated with the mRNA-1345 study injection in Part A at least 21 months prior to Screening.

4.3.2. Exclusion Criteria (Part B Substudy)

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

1. Participation in another clinical research study where participant has received an investigational product (drug/biologic/device) within 6 months before the planned date of BD study injection (BD Day 1). Current participation in another RSV investigational study is exclusionary.
2. History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
3. Certain immune-mediated conditions that are stable and well-controlled (eg, Hashimoto thyroiditis), as well as those that do not require systemic immunosuppressants per Exclusion Criterion #10 (eg, asthma, psoriasis, or vitiligo) may be permitted at the discretion of the investigator.

Note: HIV positive participants with CD4 count ≥ 350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy) as determined from participant's medical records, are permitted.

Note: To clarify, participants with stable autoimmune diseases that do not require systemic immunosuppressants (per Exclusion Criterion #10) are permitted.

4. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or any components of the mRNA-1345 vaccine.
6. Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
7. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
8. Received or plans to receive any nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 14 days before or after the BD Day 1 study injection. Nonstudy vaccination(s) should not be delayed.

   Note: Commercial influenza vaccine may be given at any time, but ideally at least 7 days before or after the BD study injection. If a participant receives an influenza vaccine, this should be captured within the concomitant medication eCRF.
9. Received or plans to receive any commercial RSV vaccination at any time prior to BD study injection (BD Day 1) or during the substudy.
10. Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the BD study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
11. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the BD study injection or during the substudy.
12. Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥ 37.8°C [100.0°F] on the planned day of BD study injection).
13. 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 substudy or could interfere with the interpretation of study results.
14. Known uncontrolled disorder of coagulation.
    Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation and under good

control will NOT be excluded.

15. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
16. Donated ≥ 450 mL of blood products < 14 days prior to Screening.
17. Member of study personnel or is an immediate family member or household member of study personnel.

4.3.3. Inclusion and Exclusion Criteria Definitions (Part B Substudy)

See Section 3.3.3 for details.

4.3.4. Participant Restrictions (Part B Substudy)

See Section 3.3.4 for details.

4.3.5. Screen Failures (Part B Substudy)

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

Participants meeting the Exclusion Criterion #12 (Section 4.3.2) of being acutely ill or febrile may be rescheduled within the relevant window periods.

4.4. Study Treatment (Part B Substudy)

4.4.1. Investigational Product (Part B Substudy)

The term “IP” refers to both mRNA-1345 vaccine and placebo administered in this substudy.

The mRNA-1345 is an LNP dispersion of mRNA sequences encoding the RSV fusion glycoprotein stabilized in the prefusion conformation, formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; DSPC; and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000.

For the Part B substudy, the mRNA-1345 vaccine will be provided as a sterile liquid for injection and will be a white to off-white dispersion, at a concentration of 0.1 mg/mL in 20 mM Tris containing 87 mg/mL sucrose and 2.2 mM acetate at pH 7.5 (Table 17).

The placebo is 0.9% sodium chloride (normal saline) injection, which meets the criteria of the USP or equivalent as per local regulations (Table 17).

The IP (mRNA-1345 or placebo) will be administered as a 0.5-mL single IM injection on BD Day 1 according to the procedures specified in the mRNA-1345-P301 Pharmacy Manual.

Table 17: Investigational Product Administered (Part B Substudy)

Vaccination Group:	Investigational Product	Placebo
Intervention Name:	mRNA-1345	0.9% Normal Saline
Type:	Vaccine	Placebo
Dosage Level:	50 µg mRNA	N/A
Route of Administration:	IM injection	IM injection
Physical Description:	Sterile liquid for injection. White to off-white dispersion	A sterile, clear solution
Source:	Centrally provided by Sponsor	Hybrid – potentially centrally and locally
Packaging and Labeling:	mRNA-1345 will be provided in 2R glass vials. Each vial will be labeled as required per country requirement	Source dependent

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid.

4.4.2. Dosing and Management of Investigational Product (Part B Substudy)

4.4.2.1. Method of Randomly Assigning Participants to Vaccination Groups (Part B Substudy)

The randomization will be in a blinded manner using a centralized IRT, in accordance with pre-generated randomization schedules. Only the unblinded personnel (Section 4.4.2.8.1) will have controlled access to vaccination group assignments.

4.4.2.2. Administration of Investigational Product (Part B Substudy)

See Section 3.4.2.2 for details and refer to the SoE for Part B (Table 22).

4.4.2.3. Delivery and Receipt (Part B Substudy)

See Section 3.4.2.3 for details.

4.4.2.4. Packaging and Labeling (Part B Substudy)

For the Part B substudy, the sterile vaccine product will be packaged in a 2R glass vial with a 0.7-mL fill volume.

See Section 3.4.2.4 for details.

4.4.2.5. Storage (Part B Substudy)

The mRNA-1345 vaccine supplied for Part B may be stored for up to 18 months at -25°C to -15°C, which includes up to 90 days of storage at 2°C to 8°C and 48 hours at 8°C to 25°C.

See Section 3.4.2.5 for details.

4.4.2.6. Investigational Product Accountability (Part B Substudy)

See Section 3.4.2.6 for details.

4.4.2.7. Handling and Disposal (Part B Substudy)

See Section 3.4.2.7 for details.

4.4.2.8. Blinding (Part B Substudy)

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

The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end. The following study or site personnel are unblinded:

- Unblinded medically qualified study or site personnel will perform IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations or assessments of any study endpoints.
- Unblinded IP accountability monitors will ensure that sites are following all proper IP accountability, preparation, and administration procedures.

4.4.2.8.1. Planned Unblinding (Part B Substudy)

To maintain an observer-blind design, investigators, study staff, participants, and Sponsor and CRO staff with oversight of study conduct will remain blinded to vaccination group allocation for the duration of Part B. All study participants will be followed for safety, immunogenicity, and RSV surveillance/infection endpoints through the planned study period and results will be summarized in an end of study report.

4.4.2.8.2. Unplanned Unblinding (Part B Substudy)

See Section 3.4.2.8.2 for details.

4.4.3. Study Treatment Compliance (Part B Substudy)

See Section 3.4.3 for details.

4.4.4. Prior and Concomitant Therapy (Part B Substudy)

4.4.4.1. Prior Medications and Therapies (Part B Substudy)

New medications (including any prescription or over-the-counter medications, vaccines, or blood products) that start after the Month 24/EOS visit of Part A and before the Screening Visit of Part B will be collected.

4.4.4.2. Concomitant Medications and Therapies (Part B Substudy)

See Section 3.4.4.2 for details.

4.4.4.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses (Part B Substudy)

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PP analysis (analysis sets are described in Section 4.7.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP 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 14 days before through 14 days after the study injection, excluding influenza vaccine that may be given anytime, but ideally at least 7 days before or after study injection.
- Any commercial RSV vaccination.
- Immunoglobulins and/or any blood products administered during the study period (except for treatment of COVID-19).
- Medications that suppress the immune system (except for treatment of COVID-19).

It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

All medication and interventions necessary for the appropriate care of the study participant, particularly to treat RSV, should be administered and appropriately documented along with the AE.

4.5. Delaying or Discontinuing Investigational Product and Participant Withdrawal from the Substudy (Part B Substudy)

4.5.1. Criteria for Delay of Investigational Product Administration (Part B Substudy)

See Section 3.5.1 for details and refer to the SoE for Part B (Table 22).

4.5.2. Participant Withdrawal from the Substudy (Part B Substudy)

See Section 3.5.2 for details.

4.5.3. Lost to Follow-up (Part B Substudy)

See Section 3.5.3 for details.

4.6. Study Assessments and Procedures (Part B Substudy)

Before undergoing any study procedures, all potential participants will sign an ICF (as detailed in Section 6.2.6). Participants will undergo study procedures at the timepoints specified in the SoE (Table 22).

A participant also can be seen for an unscheduled visit at any time during the substudy. An unscheduled visit may be prompted by reactogenicity issues, symptoms of RSV-like illness, or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with the local regulations, investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoE (Table 22). Adherence to the study design requirements is essential and required for study conduct.
- Visits (scheduled or unscheduled) may occur at the study site, mobile site, or other off-site location including the participant's home. Only the Screening and BD Day 1 visit(s) are required to occur at the study site.
- The SoE indicates the acceptable time windows around optimal timing of visits and safety contacts.
  - If a visit cannot be scheduled within the window and/or the participant misses the scheduled 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 BD Day 1.
  - Safety contacts at Day 60 and every 60 days thereafter do not need to be performed in the months in which a scheduled visit is required (information that would be collected during a safety contact can be obtained during the scheduled visit). If a safety contact cannot be made within the allowable timeframe according to the SoE, then site personnel should attempt to complete a safety contact at any other time within that calendar month.
  - If a participant misses a scheduled visit, a safety contact can be performed for that month but is not considered as a replacement for the scheduled visit.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should receive the study injection and/or continue participation in the substudy.
- 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.
- Where permitted by local regulations, 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 SoE (Table 22).

- Screening will be conducted at the Month 24/EOS visit for Part A, which may be conducted up to 3 months (90 days) early.
- Screening and BD Day 1 activities may be performed on the same day or on different days. However, BD Day 1 activities must occur within 14 days after Screening.

4.6.1. Immunogenicity Assessments (Part B Substudy)

Blood samples for immunogenicity assessments will be collected at the timepoints indicated in the SoE (Table 22). Immunogenicity assessments will include the following:

- Serum neutralizing Ab level to RSV-A and RSV-B

Serum will be tested using RSV-A and RSV-B neutralization assays as well as in a bead-based immunoassay specific to the RSV fusion glycoprotein.

Testing will be performed in laboratories designated by the Sponsor using an appropriately validated clinical assay as per regulatory guidance.

4.6.2. Safety Assessments (Part B Substudy)

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 4.6.3.5) that occur during the 7 days following BD study injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 4.6.2.2).
- Unsolicited AEs (Section 4.6.3.1) observed or reported during the 28 days following BD study injection (ie, the day of injection and 27 subsequent days).
- AEs leading to discontinuation from study participation from BD Day 1 through EOS or withdrawal from the substudy.
- MAAEs from BD Day 1 through EOS or withdrawal from the substudy.
- AESIs from BD Day 1 through EOS or withdrawal from the substudy.
- SAEs from BD Day 1 through EOS or withdrawal from the substudy.
- Vital sign measurements (Section 4.6.2.5).
- Physical examination findings (Section 4.6.2.4).
- Concomitant medications and nonstudy vaccinations (Section 4.4.4.2).

4.6.2.1. Safety Contact (Part B Substudy)

See Section 3.6.2.1 for details and refer to the SoE for Part B (Table 22).

4.6.2.2. Use of Electronic Diaries (Part B Substudy)

At the time of consent, the participants must confirm they will be willing to complete an eDiary (for 7-day reactogenicity and monthly follow-up for surveillance for respiratory disease) using

either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. If the participant is unable to complete the eDiary on their own, a caregiver can assist with the data entry, but the information entered in the eDiary must come from the participant.

Before enrollment on BD Day 1, the participant will be instructed or assisted with the download of the eDiary application on their personal smartphone or will be provided a Sponsor-provisioned device to record solicited ARs (Section 4.6.3.5) and to receive eDiary prompts for monthly surveillance for symptoms of RSV-like illness (Section 4.6.5.2).

On the day of study injection (BD Day 1), participants will be given eDiaries and trained to use them. Participants will record data into the eDiary starting approximately 60 minutes after injection under supervision of the study staff to ensure successful entry of assessments. The 60-minute assessment is an opportunity for study staff to train the participant. The study staff will perform any retraining as necessary. Study participants will continue to record in the eDiary solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of study injection and for 6 days following study injection.

The following local ARs will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (joint aches in several joints), nausea/vomiting, fever (oral temperature), and chills.

On the day of study injection (BD Day 1), participants will be instructed 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 to the side of injection.

Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.

All medications taken on the day of study injection and during the 28 days after the study injection (ie, the day of injection and 27 subsequent days) should be reported in the eDiary. Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on the day of study injection or for the 6 subsequent days.

Solicited local and systemic reactogenicity ARs, as defined in Section 4.6.3.5, will be collected on the day of study injection and during the 7 days after the study injection (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in an eDiary until it is no longer reported, not to exceed 28 days after the study injection. ARs recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or electronic means or at the following study visit, or during an unscheduled visit. (Table 22).

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

If a participant does not respond to the monthly eDiary prompt within 2 days after the scheduled timepoint, the study staff will follow-up directly with the participant via telephone call or other electronic means to confirm their health status and to remind the participant of the importance of maintaining monthly contact via the eDiary prompt.

4.6.2.3. Demographics/Medical History (Part B Substudy)

Demographic information was recorded for Part A and will not be recorded again for Part B.

New medical conditions or significant medical events that occur after the Month 24/EOS visit of Part A and before the Screening Visit of Part B will be added as medical history for Part B.

Receipt of seasonal influenza vaccine during the current influenza season will be recorded as a concomitant medication; other prior and concomitant medications will be recorded as described (Section 4.4.4).

4.6.2.4. Physical Examination (Part B Substudy)

See Section 3.6.2.4 for details.

4.6.2.5. Vital Sign Measurements (Part B Substudy)

See Section 3.6.2.5 for details and refer to the SoE for Part B (Table 22).

4.6.2.6. Blood Sampling Volumes (Part B Substudy)

See Section 3.6.2.6 for details.

4.6.3. Safety Definitions and Procedures (Part B Substudy)

4.6.3.1. Adverse Event (Part B Substudy)

See Section 3.6.3.1 for details.

4.6.3.2. Medically-Attended Adverse Events (Part B Substudy)

See Section 3.6.3.2 for details.

4.6.3.3. Adverse Events of Special Interest (Part B Substudy)

See Section 3.6.3.3 for details.

4.6.3.3.1. Anaphylaxis (Part B Substudy)

See Section 3.6.3.3.1 for details.

4.6.3.3.2. Myocarditis/Pericarditis/Myopericarditis (Part B Substudy)

See Section 3.6.3.3.2 for details.

4.6.3.4. Serious Adverse Events (Part B Substudy)

See Section 3.6.3.4 for details.

4.6.3.5. Solicited Adverse Reactions (Part B Substudy)

See Section 3.6.3.5 for details.

4.6.3.6. Recording and Follow-up of an AE and/or SAE (Part B Substudy)

See Section 3.6.3.6 for details and refer to the SoE for Part B (Table 22)

4.6.3.7. Time Period and Frequency for Collecting AE, AESI, and SAE Information (Part B Substudy)

See Section 3.6.3.7 for details.

4.6.3.8. Assessment of Intensity (Part B Substudy)

See Section 3.6.3.8 for details.

4.6.3.9. Assessment of Causality (Part B Substudy)

See Section 3.6.3.9 for details.

4.6.3.10. Reporting Adverse Events (Part B Substudy)

See Section 3.6.3.10 for details.

4.6.3.11. Regulatory Reporting Requirements for SAEs (Part B Substudy)

See Section 3.6.3.11 for details.

4.6.4. Monitoring Committees (Part B Substudy)

4.6.4.1. Internal Safety Team (Part B Substudy)

Safety will be closely monitored and reviewed by the ongoing IST.

4.6.4.2. Independent Cardiac Event Adjudication Committee (Part B Substudy)

See Section 3.6.4.3 for details.

4.6.5. RSV Case Detection (Part B Substudy)

4.6.5.1. RSV Disease Definitions (Part B Substudy)

Part B will use the same definitions of RSV-LRTD with 2 or more symptoms, RSV-LRTD with 3 or more symptoms, and RSV-ARD that were used in evaluate efficacy in Part A. See Section 3.6.1.1 for details.

4.6.5.2. Surveillance for RSV-Like Illness (Part B Substudy)

Starting from 14 days after the BD study injection and until EOS, participants will enter an active and passive surveillance period for respiratory disease. Participants will be given and trained to use an eDiary as described in Section 4.6.2.2 for monthly surveillance of respiratory symptoms. Surveillance will include the following:

- Provision of a Participant ID Card, which provides details on study participation, site contact information, and a list of symptoms of respiratory disease. Participants should present this card to HCPs not affiliated with the substudy who encounter participants with symptoms of respiratory disease.
- The eDiary will provide monthly prompts (every 30 days) to elicit symptoms of RSV-like illness (new onset or worsening) and exposure to individuals with known RSV. The monthly eDiary prompt will inquire about the following:
  - Changes in health since the last time completing the monthly eDiary prompt or the last contact with the study staff.
  - Capture of any respiratory symptoms currently being experienced or experienced since the last time completing the monthly check-in as defined in Section 4.6.5.2.
  - Any contact with a healthcare provider that may indicate a MAAE.
- Participants are encouraged to respond to the eDiary as soon as possible if they have any symptom. If they do not have symptoms, they are encouraged to respond to the eDiary prompt at the end of the month from the trigger. Participants will be contacted by the study staff if they have missed reporting in the eDiary.
- If a participant reports RSV-like symptoms prior to the active and passive surveillance period (which starts 14 days after study injection), the site staff should still arrange an illness visit; this is not considered a protocol deviation.
- If symptoms arise or worsen after the participant has completed the eDiary entry for a given month, the participant should contact the site staff to report symptoms of RSV-like illness.
- If symptoms or worsening symptoms are reported, study staff will arrange an unscheduled visit with the participant, if possible, within 5 days after symptom onset or worsening for medical evaluation and nasopharyngeal swab collection. If the swab sample cannot be collected within 5 days after symptom onset or worsening, the sample may still be collected at the discretion of the site investigator if symptoms are still present (similarly, if symptoms are noted on BD Day 8, swab samples should still be collected even though this is within the 14 days after injection). Clinical information will be collected to evaluate the severity of the case. If the participant visited an external HCP because of the reported symptoms, site personnel are encouraged to obtain information from the HCP.
- All efforts must be made to collect a nasopharyngeal swab within 5 days of symptom onset for medical evaluation; however, if 5 days have elapsed since first symptom onset, swabs should still be collected as soon as possible, and this is not considered a protocol deviation.

Respiratory disease will be defined by a new onset or worsening (> 24 hours) of one or more of any of the following:

- Rhinorrhea
- Nasal congestion

- Pharyngitis (sore throat)
- Cough
- New or increased wheezing
- New or increased shortness of breath
- Tachypnea (≥ 20 breaths per minute)
- New or increased sputum production or a change in the volume or character of sputum
- Fever (≥ 37.8°C [100.0°F])
- Chills
- Hoarseness
- Sinus pain
- Pleuritic chest pain

"New onset" will require at least a 14-day period free of symptoms or with baseline symptoms, to differentiate an episode from any prior acute illness. "Worsening" will require > 24 hours of worsening of a chronic symptom (eg, worsening cough in a person with a chronic cough) or the occurrence of additional new or intensified respiratory symptoms. When any participant is determined to have a new or worsening respiratory disease, the participant will be invited to have an unscheduled visit and will be evaluated (and tested, if RSV is suspected). During this visit (unscheduled visit), which will occur within 5 days, if possible, of symptom onset or worsening, the following assessments will be performed:

- Review and confirmation of the history of respiratory disease, including approximate date of onset or worsening of respiratory disease and solicitation of each of the above-listed symptoms. Participants will also be asked about exposure to individuals with known RSV infection.
- Vital signs measurements, including resting respiratory rate and oxygen saturation (on room air or the participant's basal level of chronic supplemental oxygen use), which will be captured as numerical values.
- Ascertainment of any visits to nonstudy HCPs, including a healthcare visit by the participant, a mobile/home visit by an HCP, or emergency room/urgent healthcare visit in response to the episode of respiratory disease. Site personnel are encouraged to attempt to obtain information from the HCPs.
- Ascertainment of hospital admission or prolongation of existing hospital stay in response to the episode of respiratory disease. Reporting procedures for SAEs should be followed (Section 4.6.3.10).
- Ascertainment of new concomitant medications (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from the respiratory disease.
- Collection of a specimen of upper respiratory secretions via nasopharyngeal swabs for

detection of respiratory pathogens by reverse transcriptase polymerase chain reaction (RT-PCR) including coronavirus (229E, HKU1, NL63, OC43); human metapneumovirus; human rhinovirus/enterovirus; adenovirus; influenza A; influenza A H1; influenza A H1-2009; influenza A H3; influenza B; parainfluenza virus 1; parainfluenza virus 2; parainfluenza virus 3; parainfluenza virus 4; RSV-A; RSV-B; Chlamydia pneumoniae; Mycoplasma pneumoniae; and SARS-CoV-2. Data from specimens obtained using an RSV diagnostic test at a healthcare visit external to the study or mobile site may be accepted if the results are obtained using FDA-approved kits or have laboratory developed tests within laboratories that are CLIA-certified.

Note: RT-PCR testing for RSV and other pathogens by the study laboratory will be for the purposes of this protocol and not for clinical care. Conversely, local laboratory results, while informative to the clinician, will not be included as an endpoint for this substudy, unless the presence of RSV or other pathogen infection is diagnosed using an assay pertinent to state and federal regulations (eg, local CLIA-certified or a regulated laboratory). Data from specimens obtained using an RSV diagnostic test at a healthcare visit external to the study or mobile site may be accepted.

Participants will continue to complete the eDiary for ascertainment of respiratory symptom status. Subsequently, the study staff will contact the participants weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or through 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications. This follow-up will occur regardless of whether the participant had a positive test for RSV.

All clinical findings will be recorded in the eCRF.

4.6.5.3. Ancillary Supplies for Participant Use (Part B Substudy)

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions for recording solicited ARs in eDiaries (Section 4.6.2.2). Based on availability, ePRO devices may be provided to those participants who do not have their own device to use for eDiary activities.

4.6.5.4. Hospitalization (Part B Substudy)

For hospital stays (new hospitalization or prolongation of existing hospitalization) resulting from symptoms of RSV including study endpoints (LRTD, ARD) or for AEs that qualify as SAEs due to hospitalization or prolongation of existing hospitalization, pertinent information will be collected via initial and updated reports to the safety database. Information to be collected for hospitalizations due to respiratory symptoms are described in Section 4.6.5.2. Regulatory reporting requirements must be observed for all SAEs (Section 4.6.3.11).

4.6.6. Management of Overdose (Part B Substudy)

See Section 3.6.5 for details.

4.6.7. Pharmacokinetics (Part B Substudy)

Pharmacokinetic parameters are not evaluated in this substudy.

4.6.8. Pharmacodynamics (Part B Substudy)

Pharmacodynamic parameters are not evaluated in this substudy.

4.6.9. Exploratory Assessments and Biomarkers (Part B Substudy)

Exploratory objectives are listed in Section 4.1.3. Immunogenicity assessments and RSV case detection are described in Sections 4.6.1 and 4.6.5, respectively.

4.7. Statistical Considerations (Part B Substudy)

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

4.7.1. Blinding and Responsibility for Analyses (Part B Substudy)

Blinding during the Part B substudy will be conducted as described in Section 4.4.2.8.

Planned primary and final analyses are described in Section 4.7.6. The independent unblinded statistician(s) and statistical programmer(s) performing the primary and final analyses will have no other responsibilities associated with the study. Prespecified Sponsor team members will be unblinded for these analyses. Participants and investigators will remain blinded until the end of the substudy.

4.7.2. Statistical Hypotheses (Part B Substudy)

Hypothesis testing will be conducted as described in Section 4.7.6.2.

The 2 coprimary immunogenicity objectives aim to demonstrate noninferiority of the serum RSV-A and RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose. These objectives are supported by 2 coprimary endpoints, comparing the RSV-A and RSV-B GMTs at BD Day 29 to the RSV-A and RSV-B GMTs at Primary Dose Day 29.

Primary Hypotheses:

Null hypothesis H^{b1}_0: Immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-A nAb at BD Day 29, is inferior compared with the GMT of RSV-A nAb at Primary Dose Day 29. The first coprimary objective is considered met if noninferiority of the GMT of RSV-A nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the GMR rules out 0.667 [ie, LB > 0.667] using a noninferiority margin of 1.5). GMR is the ratio of GMT of RSV-A nAb at BD Day 29 to Primary Dose Day 29.

Null hypothesis H^{b2}_0: Immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-B nAb at BD Day 29, is inferior compared with the GMT of RSV-B nAb at Primary Dose Day 29. The second coprimary objective is considered met if noninferiority of the GMT of RSV-B nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the GMR rules out 0.667 [ie, LB > 0.667] using a noninferiority margin of 1.5). GMR is the ratio of GMT of RSV-B nAb at BD Day 29 to Primary Dose Day 29.

Secondary Hypotheses:

Null hypothesis H^{b3}_0: Immunogenicity response to a BD of mRNA-1345, as measured by SRR of RSV-A nAb at BD Day 29, is inferior compared with the SRR of RSV-A nAb at Primary Dose Day 29. This secondary objective is considered met if noninferiority of the SRR of RSV-A nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the SRR difference rules out 10% [ie, LB > -10%] using a noninferiority margin of 10%). The SRR difference is SRR of RSV-A nAb at BD Day 29 minus the SRR of RSV-A nAb at Primary Dose Day 29.

Null hypothesis H^{b4}_0: Immunogenicity response to a BD of mRNA-1345, as measured by SRR of RSV-B nAb at BD Day 29, is inferior compared with the SRR of RSV-B nAb at Primary Dose Day 29. This secondary objective is considered met if noninferiority of the SRR of RSV-B nAb at BD Day 29 is demonstrated (ie, the LB of the 95% CI of the SRR difference rules out 10% [ie, LB > -10%] using a noninferiority margin of 10%). The SRR difference is SRR of RSV-B nAb at BD Day 29 minus the SRR of RSV-B nAb at Primary Dose Day 29.

4.7.3. Sample Size Determination (Part B Substudy)

This substudy will plan to randomize approximately 1500 participants in a 2:1 randomization ratio to the mRNA-1345 or the placebo groups. Therefore, approximately 1000 participants will be randomized to the mRNA-1345 group and 500 participants will be randomized to the placebo group.

With approximately 1000 participants randomized to mRNA-1345, the substudy has approximately 95% probability to observe at least 1 participant in the group with an AE at a true 0.3% AE rate.

Considering an estimated 10% of participants who may be ineligible for inclusion in the PP Set, there are 900 eligible participants for immunogenicity analysis in mRNA-1345 group.

Statistical power for testing primary hypotheses H^{b1}_0 and H^{b2}_0:

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-A nAb at BD Day 29, compared with the GMT of RSV-A nAb at Primary Dose Day 29, using a paired t-test at a 2-sided alpha of 0.05. The assumptions are: the true GMT ratio (GMT of RSV-A nAb at BD Day 29 to Primary Dose Day 29) is 0.8, the standard deviation of the natural log-transformed titer is 1.5, with a noninferiority margin of 1.5.

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by GMT of RSV-B nAb at BD Day 29, compared with the GMT of RSV-B nAb at Primary Dose Day 29, using a paired t-test at a 2-sided alpha of 0.05. The assumptions are: the true GMT ratio (GMT of RSV-B nAb at BD Day 29 to Primary Dose

Day 29) is 0.8, the standard deviation of the natural log-transformed titer is 1.5, with a noninferiority margin of 1.5.

The global power considering meeting both coprimary objectives is at least 90%.

Statistical Power for testing secondary hypotheses H^{b3}_0 and H^{b4}_0:

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by SRR of RSV-A nAb at BD Day 29, compared with the SRR of RSV-A nAb at Primary Dose Day 29, using the normal approximation method to test for difference in paired proportions at a 2-sided alpha of 0.05. The assumptions are: the true SRR difference (SRR of RSV-A nAb at BD Day 29 minus SRR of RSV-A nAb at Primary Dose Day 29) is -5%, the proportion of discordant pairs is 15%, with a noninferiority margin of 10%.

There is at least 95% power to demonstrate the noninferiority of the immunogenicity response to a BD of mRNA-1345, as measured by SRR of RSV-B nAb at BD Day 29, compared with the SRR of RSV-B nAb at Primary Dose Day 29, using the normal approximation method to test for difference in paired proportions at a 2-sided alpha of 0.05. The assumptions are: the true SRR difference (SRR of RSV-B nAb at BD Day 29 minus SRR of RSV-B nAb at Primary Dose Day 29) is -5%, the proportion of discordant pairs is 15%, with a noninferiority margin of 10%.

4.7.4. Analysis Populations (Part B Substudy)

Analysis populations for statistical analyses are Randomization Set, FAS, PP Set, Solicited Safety Set, and Safety Set, as shown in Table 18.

Table 18: Populations for Analyses (Part B Substudy)

Population	Description
Randomization Set	All participants who are randomized in the Part B substudy, regardless of the participant's IP administration status. Participants will be included in the vaccination group to which they are randomized.
FAS	All Part B randomized participants who receive any IP. Participants will be analyzed according to the vaccination group to which they are randomized.
PP Set	All participants in the FAS who receive both the Part A and Part B assigned IP doses according to protocol, have RSV immunogenicity titer results at pre-Primary Dose (baseline) (prior to the primary IP administration), have RSV immunogenicity titer results at Primary Dose Day 29, have at least 1 valid result at BD Day 29, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined prior to database lock and unblinding. The PP Set will be the primary population used for immunogenicity analyses. Participants will be analyzed according to the vaccination group to which they are randomized.
Solicited Safety Set	All Part B randomized participants who receive any IP and contribute any solicited AR data.

Population	Description
	The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the IP that they actually receive.
Safety Set	All Part B randomized participants who receive any IP. The Safety Set will be used for all analyses of safety. Participants will be included in the vaccination group corresponding to the IP that they actually receive.

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

4.7.5. Statistical Analyses (Part B Substudy)

This section provides a summary of the planned statistical analyses of the coprimary and secondary immunogenicity endpoints.

All analyses will be performed by vaccination group, unless specified otherwise. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

4.7.5.1. Immunogenicity Analyses (Part B Substudy)

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

The coprimary endpoints, the GMR of RSV-A nAb or RSV-B nAb titers at BD Day 29 to Primary Dose Day 29, will be estimated by back transforming the mean of the paired difference of RSV-A nAb or RSV-B nAb within the booster vaccination group on the logarithmic scale between BD Day 29 and Primary Dose Day 29. The 95% CI for the GMR will be based on the paired t-test of the log-transformed values then back transformed to the original scale for presentation. For each coprimary endpoint, the noninferiority of GMT at BD Day 29 will be demonstrated if the LB of 95% CI for the GMR is > 0.667. GMT and corresponding 95% CI for RSV-A nAb or RSV-B nAb titers at BD Day 29 will be summarized descriptively by vaccination group.

The SRR of RSV-A nAb or RSV-B nAb, is defined as the proportion of participants with post-BD titers ≥ 4 × LLOQ if baseline is < LLOQ or a ≥ 4-fold increase from baseline if baseline is ≥ LLOQ. Baseline value is defined as the most recent nonmissing immune measurements collected before the mRNA-1345 primary dose.

The secondary endpoints, SRR difference and 95% CI of RSV-A nAb or RSV-B nAb at BD Day 29 and at Primary Dose Day 29, will be estimated through a logistic model with repeated measure adjusted for the within-participant correlation. The noninferiority of SRR at BD Day 29 will be demonstrated if the LB of 95% CI for SRR difference is > -10%.

In addition, data from immunogenicity assays will be summarized for each vaccination group using SRR and GMT with 95% CIs, for each timepoint for which an assessment is performed.

For the immunogenicity endpoints, GMT of nAb titers with corresponding 95% CI at each timepoint and GMFR of specific Ab titers with corresponding 95% CI at each post-BD timepoint over pre-Primary Dose (baseline) will be provided by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For summaries of GMTs, 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, unless otherwise specified.

Proportion of participants with seroresponse will be provided with 2-sided 95% CI using the Clopper-Pearson method by postbaseline timepoint.

Further details, including the participant sampling plan, will be described in the SAP.

4.7.5.2. Safety Analyses (Part B Substudy)

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group.

4.7.5.2.1. Adverse Events (Part B Substudy)

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, vital signs, and physical examination findings.

Unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used in this substudy for the collection and severity grading of solicited ARs.

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

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, AESIs, severe AEs, and AEs leading to discontinuation from the substudy will be summarized. Number of events of unsolicited AEs, SAEs, MAAEs, and AESIs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 19 summarizes analysis strategy for safety parameters. Further details will be described in the SAP.

Table 19: Analysis Strategy for Safety Parameters (Part B Substudy)

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any AESI	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically-attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by system organ class and preferred term coded by MedDRA.

4.7.5.2.2. Baseline Descriptive Statistics (Part B Substudy)

Demographic variables (eg, age, height, weight, and body mass index) and baseline characteristics will be summarized by vaccination group using descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

4.7.5.3. Exploratory Analyses (Part B Substudy)

Analyses of exploratory endpoints will be described in the SAP.

4.7.6. Planned Analyses (Part B Substudy)

4.7.6.1. Interim Analyses (Part B Substudy)

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

The final analysis of all endpoints will be performed after all participants have completed the BD Day 181/EOS visit. Results of this analysis will be presented in a final CSR. The final CSR will include full analyses of all safety, immunogenicity, and RSV surveillance/infection data through BD Day 181/EOS.

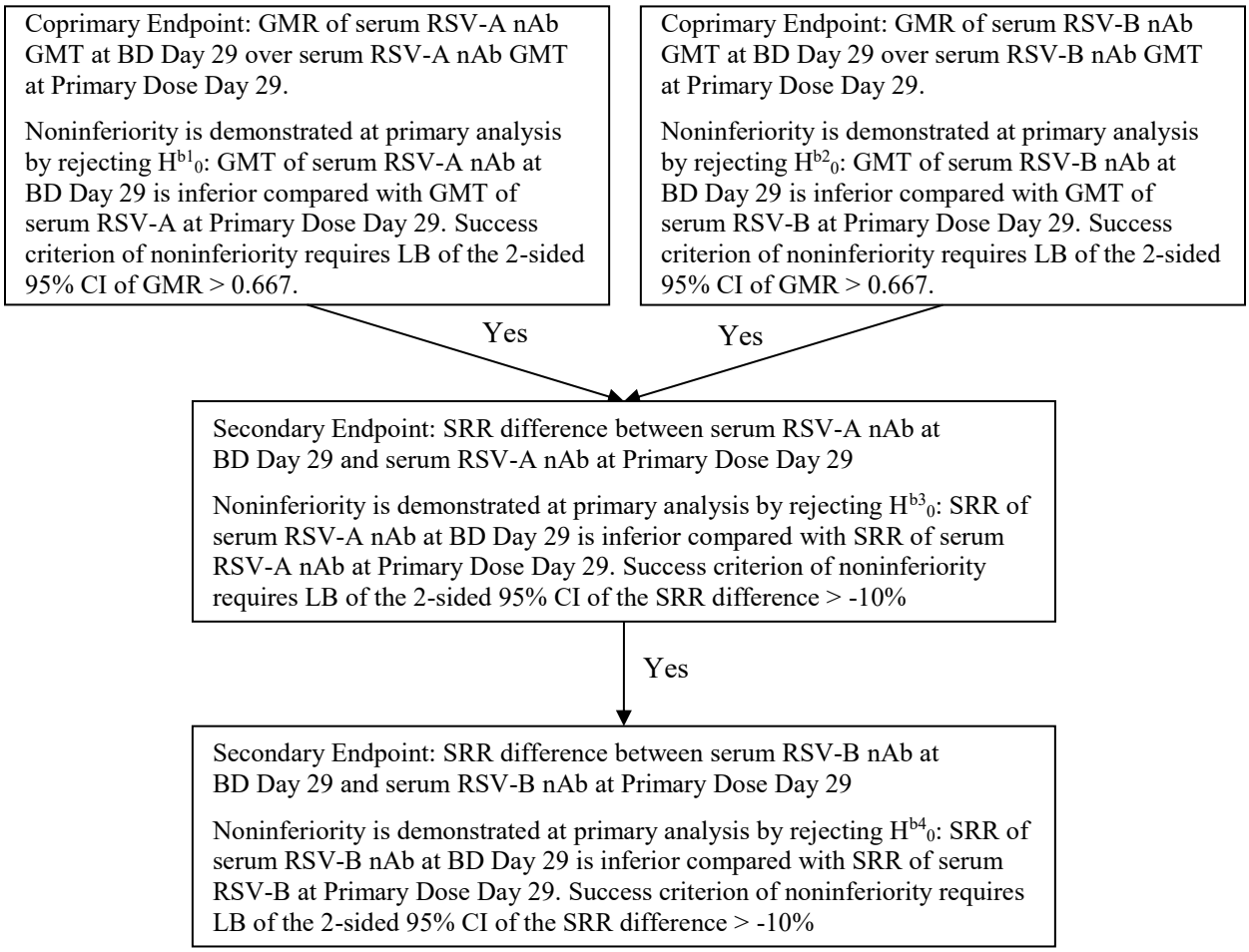
4.7.6.2. Multiplicity (Part B Substudy)

A sequential/hierarchical testing procedure as shown in Figure 6 will be used to control type 1 error rate at 5% (2-sided) over the 2 coprimary and 2 secondary immunogenicity endpoints.

The coprimary endpoints will be tested at the planned primary analysis based on a 2-sided type 1 error rate of 0.05. The success criteria of the 2 coprimary endpoints in Part B need to be met successfully to declare the noninferiority of the BD is achieved.

The 2 secondary endpoints on SRR at Day 29 will be tested at a 2-sided type 1 error rate of 0.05 when both coprimary endpoints have achieved statistical significance.

Figure 6: Testing Sequence of the Primary, and Secondary Endpoints (Part B Substudy)



Abbreviations: BD = booster dose; CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LB = lower bound; nAb = neutralizing antibody; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate.

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6. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

6.1. APPENDIX 1: Schedule of Events

If a participant cannot attend a study site visit (scheduled or unscheduled, with the exception of final eligibility and Day 1 visit), a mobile visit is acceptable if performed by appropriately delegated study staff or a mobile healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a mobile visit to the participant is possible (with the exception of the Day 1 visit), a safety contact should be performed that includes the assessments scheduled for the safety contact.

See Table 20 and Table 21 for the Part A Phase 2 and Phase 3 SoEs, respectively, and Table 22 for the Part B SoE (select US sites only).

Table 20: Schedule of Events (Part A Phase 2 Segment)

Visit Number		1		2	3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	V[1]	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Informed consent form, demographics, medical history	X										
Confirmation of inclusion/exclusion criteria	X	X									
Physical examination[4]	X	X									
Vital signs[5]	X	X									X
Randomization		X									
Serum (Ab)		X[6]		X	X		X	X	X	X[7]	
Study injection[8]		X									
eDiary activation for recording solicited ARs (7 days) and 60-minute post-injection solicited AR assessments, vital signs, and eDiary entry review[9]		X									

Visit Number		1		2	3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	V[1]	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Review of eDiary for recording solicited ARs			X								
RSV diagnostic test[10]											X
Surveillance											
eDiary activation for safety follow-up (surveillance of RSV-like illness)[11]				X							
eDiary weekly prompts for safety follow-up (to solicit symptoms of RSV-like illness)[11]				Weekly eDiary prompts[12]							
Unscheduled visit (for RSV-like symptoms)[11]											X
Passive surveillance[13]				X	X	X	X	X	X	X	
RSV symptom log[14]											X
Nasopharyngeal swab for virus detection[15]											X
Follow-up safety contact[16]			X			X					X[14]
Collection of Edmonton Frail Scale[17]		X						X		X	
eDiary collection of EQ-5D-5L[18]		X		eDiary prompts[12,19]							
eDiary collection of WPAI[20]		X		eDiary prompts[12,21]							
Recording of unsolicited AEs		X	X	X	X						

Visit Number		1		2	3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	V[1]	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Recording of MAAEs, AESIs/SAEs, or AEs leading to study withdrawal, hospitalizations or outpatient treatment-related to or for the treatment of the MAAE/AESI/SAE[22,23]		X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[22]	X	X	X	X	X	X	X	X	X	X	X
Study completion										X	

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse events of special interest; AR = adverse reaction; CLIA = Clinical Laboratory Improvement Amendment; D = day; eCRF = electronic case report form; eDiary = electronic diary; EOS = end of study; EQ-5D-5L = Five Level EuroQol 5-Dimension; EQ VAS = EuroQol visual analogue scale; HRQoL = health-related quality of life; IM = intramuscular; IP = investigational product; M = month; MAAE = medically-attended adverse event; NA = not applicable; RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety contact; USIV = unscheduled illness visit; V = in-person visit; WPAI = Work Productivity and Activity Impairment Questionnaire.

1. All study visits with the exception of final eligibility and Day 1 visit can take place at the study or mobile site or at the home of the participant, where allowed by local regulations. 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. For a subset of participants at select US sites who consent to participate in the Part B substudy, the Month 24/EOS visit may be conducted up to 3 months (90 days) early; this is not considered a protocol deviation.
2. Screening and Day 1 assessments may be performed on the same day or on different days. Additionally, the Screening visit may be performed over multiple visits if within the 14-day screening window.
3. The safety contact should occur on Day 60 and then monthly (ie, every 30 days) thereafter, but if there is a scheduled visit performed in the month then no safety contact is needed in that month. If a safety contact cannot be made in a given month, due to any reason, then the site should attempt to complete the safety contact at any other time within that calendar month. If a participant misses a scheduled visit in the month, then a safety contact should be conducted for that month but is not considered as a replacement for the missed visit.
4. A full physical examination, including height and weight (body mass index will be calculated), will be performed at the Screening visit, and symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the discretion of the

investigator. On the day of study injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

5. Vital signs measurements include assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation. The preferred route of temperature assessment is oral. Fever is defined as a body temperature ≥ 37.8°C/100.0°F. The participant will be seated for at least 5 minutes before all measurements are taken. On Day 1, vital sign measurements will be collected once before the study injection and at least 60 minutes after the study injection (before participants are discharged from the study site). Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.
6. Baseline immunogenicity sample must be collected prior to study injection.
7. In cases when EOS is the early termination visit, immunogenicity samples should be taken at this unscheduled visit.
8. All participants will be randomly assigned to receive a single IM injection of the IP (either mRNA-1345 or placebo).
9. On the day of study injection (Day 1), participants will be given eDiaries and trained to use them. Participants will record data into the eDiary starting approximately 60 minutes after injection under supervision of the study staff to ensure successful entry of assessments. Study participants will continue to record in the eDiary solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of study injection and for 6 days following study injection. Any solicited AR that is ongoing beyond Day 7 will be reported in an eDiary until it is no longer reported, not to exceed 28 days after the study injection. Participants will be given thermometers to measure their temperature and rulers to measure the injection site reactions. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or other electronic means or at the following study visit, or during an unscheduled visit.
10. Sites should attempt to collect data from tests conducted for RSV illness if CLIA-certified and available to include in the eCRF when the testing is done outside the study site for the RSV illness.
11. The eDiary will be activated for collection of RSV-like symptoms or respiratory disease every week starting at Day 15 (14 days after the study injection) and lasting until Day 730. The eDiary will provide weekly prompts (every 7 days) to elicit symptoms of RSV-like illness and exposure to individuals with known RSV. If symptoms occur, study staff will arrange an unscheduled visit with the participant. The unscheduled visit will be performed at the study or mobile site or the participant's home, where allowed by local regulations, within 5 days of symptom onset for medical evaluation and nasopharyngeal swab collection. Additionally, clinical information will be collected to evaluate the severity of the clinical case. All participants who report symptoms of RSV-like illness will receive eDiary prompts to complete the PRO questionnaires.
12. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry, but the information entered in the eDiary must come from the participant.
13. Participants can call the site at any time starting Day 15 after their injection to report any RSV-like illness/symptoms. If it is in between prompts the participant should not wait until the next prompt to report the symptoms. A visit should be arranged for medical evaluation and to obtain a nasopharyngeal swab within 5 days, if possible, after symptom onset or worsening.
14. Participants who develop RSV-like illness and provide a nasopharyngeal swab specimen will be contacted weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or through 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications.
15. Nasopharyngeal swab samples will be tested for the presence of RSV, SARS-CoV-2, and other respiratory pathogens by RT-PCR. Data from specimens obtained at a healthcare visit external to the study or mobile site may be accepted.
16. Medically qualified study staff will contact all participants. The participant will be interviewed according to the script and information will be collected about occurrence of unsolicited AEs through 28 days post-vaccination, AESIs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations.
17. The Edmonton Frail Scale will be used to assess participant frailty status at baseline, 12 months, and 24 months. Responses will be recorded on the appropriate eCRF page.
18. EQ-5D-5L is a well-validated, reliable, standardized instrument for measuring non-disease-specific HRQoL. EQ-5D-5L consists of a short descriptive system questionnaire and a visual analogue scale (EQ VAS). The short descriptive questions are designed to assess 5 dimensions of health including mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. The EQ VAS records the health status on a scale between 0 and 100, with 0 indicating the worst imaginable health and 100 indicating the best imaginable health.

19. All participants will receive eDiary prompts to complete the EQ-5D-5L questionnaire quarterly. For participants reporting symptoms of RSV-like illness, the EQ-5D-5L responses will be collected using the eDiary on the day that the symptoms start (up to 1 additional day), and at 4 days (± 1 day) and 14 days (± 1 day) after the start of the symptoms.
20. WPAI consists of 6 questions, which can quantitatively assess the amount of absenteeism, presenteeism, overall work impairment, and activity impairment attributable to a patient's health issues based on a 1-week recall period. The WPAI is available in different versions, such as WPAI, which can be adapted to a specific disease.
21. For participants reporting symptoms of RSV-like illness, the WPAI over the previous 7 days will be collected using the eDiary at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms.
22. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after the study injection; all concomitant medications relevant to or for the treatment of an AESI, SAE, or MAAE will be recorded from Screening through Day 730.
23. All hospitalizations, outpatient/physician visits and emergency room/urgent care visits associated with MAAEs or SAEs will be recorded from Day 1 through Day 730.

Table 21: Schedule of Events (Part A Phase 3 Segment)

Visit Number		1			3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	SC	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Informed consent form, demographics, medical history	X										
Confirmation of inclusion/exclusion criteria	X	X									
Physical examination[4]	X	X									
Vital signs[5]	X	X									X
Randomization		X									
Serum (Ab)		X[6]			X		X	X	X	X[7]	
Study injection[8]		X									
eDiary activation for recording solicited ARs (7 days) and 60-minute post-injection solicited AR assessments, vital signs, and eDiary entry review[9]		X									

Visit Number		1			3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	SC	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Review of eDiary for recording solicited ARs			X								
RSV diagnostic test[10]											X
Surveillance											
eDiary activation for safety follow-up (surveillance of RSV-like illness)[11]				X							
eDiary weekly prompts for safety follow-up (to solicit symptoms of RSV-like illness)[11]				Weekly eDiary prompts[12]							
Unscheduled visit (for RSV-like symptoms)[11]											X
Passive surveillance[13]				X	X	X	X	X	X	X	
RSV symptom log[14]											X
Nasopharyngeal swab for virus detection[15]											X
Follow-up safety contact[16]			X	X		X					X[14]
Collection of Edmonton Frail Scale[17]		X						X		X	
eDiary collection of EQ-5D-5L		X		eDiary prompts[12,18]							
eDiary collection of WPAI		X		eDiary prompts[12,19]							
Recording of unsolicited AEs		X	X	X	X						

Visit Number		1			3		4	5	6	7	USIV
Type of Visit/Contact	V	V	SC	SC	V[1]	SC	V[1]	V[1]	V[1]	V[1]	V[1]
Month Timepoint	NA				M1	Up to M24	M6	M12	M18	M24	Up to M24
Visit Day	Screening[2]	D1 (Baseline)[2]	D8	D15	D29	D60 then monthly[3]	D181	D365	D546	D730/ EOS	NA
Window Allowance (Days)	-14		+3	+3	+5		±14	±14	±14	±14	NA
Recording of MAAEs, AESIs/SAEs, or AEs leading to study withdrawal, hospitalizations or outpatient treatment-related to or for the treatment of the MAAE/AESI/SAE[20,21]		X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[20]	X	X	X	X	X	X	X	X	X	X	X
Study completion										X	

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse events of special interest; AR = adverse reaction; CLIA = Clinical Laboratory Improvement Amendment; D = day; eCRF = electronic case report form; eDiary = electronic diary; EOS = end of study; EQ-5D-5L = Five Level EuroQol 5-Dimension; EQ VAS = EuroQol visual analogue scale; HRQoL = health-related quality of life; IM = intramuscular; IP = investigational product; M = month; MAAE = medically-attended adverse event; NA = not applicable; RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety contact; USIV = unscheduled illness visit; V = study visit; WPAI = Work Productivity and Activity Impairment Questionnaire.

1. All study visits with the exception of final eligibility and Day 1 visit can take place at the study or mobile site or at the home of the participant, where allowed by local regulations. 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. For a subset of participants at select US sites who consent to participate in the Part B substudy, the Month 24/EOS visit may be conducted up to 3 months (90 days) early; this is not considered a protocol deviation.
2. Screening and Day 1 assessments may be performed on the same day or on different days. Additionally, the Screening visit may be performed over multiple visits if within the 14-day screening window.
3. The safety contact should occur on Day 60 and then monthly (ie, every 30 days) thereafter, but if there is a scheduled visit performed in the month then no safety contact is needed in that month. If a safety contact cannot be made in a given month, due to any reason, then the site should attempt to complete the safety contact at any other time within that calendar month. If a participant misses a scheduled visit in the month, then a safety contact should be conducted for that month but is not considered as a replacement for the missed visit. If the patient calls the site to report RSV-like symptoms, this phone call should be recorded as an unscheduled safety call.

4. A full physical examination, including height and weight (body mass index will be calculated), will be performed at the Screening visit, and symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the discretion of the investigator. On the day of study injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.
5. Vital signs measurements include assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation. The preferred route of temperature assessment is oral. Fever is defined as a body temperature ≥ 37.8°C/100.0°F. The participant will be seated for at least 5 minutes before all measurements are taken. On Day 1, vital sign measurements will be collected once before the study injection and at least 60 minutes after the study injection (before participants are discharged from the study site). Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.
6. Baseline immunogenicity sample must be collected prior to study injection.
7. In cases when EOS is the early termination visit, immunogenicity samples should be taken at this unscheduled visit.
8. All participants will be randomly assigned to receive a single IM injection of the IP (either mRNA-1345 or placebo).
9. On the day of study injection (Day 1), participants will be given eDiaries and trained to use them. Participants will record data into the eDiary starting approximately 60 minutes after injection under supervision of the study staff to ensure successful entry of assessments. Study participants will continue to record in the eDiary solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of study injection and for 6 days following study injection. Any solicited AR that is ongoing beyond Day 7 will be reported in an eDiary until it is no longer reported, not to exceed 28 days after the study injection. Participants will be given thermometers to measure their temperature and rulers to measure the injection site reactions. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or other electronic means or at the following study visit, or during an unscheduled visit.
10. Sites should attempt to collect data from tests conducted for RSV illness if CLIA-certified and available to include in the eCRF when the testing is done outside the study site for the RSV illness.
11. The eDiary will be activated for collection of RSV-like symptoms or respiratory disease every week starting at Day 15 (14 days after the study injection) and lasting until Day 730. The eDiary will provide weekly prompts (every 7 days) to elicit symptoms of RSV-like illness and exposure to individuals with known RSV. If symptoms or worsening symptoms occur, study staff will arrange an unscheduled visit with the participant. The unscheduled visit will be performed at the study site or alternate location, where allowed by local regulations, if possible within 5 days after symptom onset or worsening for medical evaluation and nasopharyngeal swab collection. If the swab sample cannot be collected within 5 days after symptom onset or worsening, the sample may still be collected at the discretion of the site investigator if symptoms are still present (similarly, if symptoms are noted on Day 8 or Day 15, swab samples should still be collected even through this is within the 14 days after injection). Reports from external healthcare provider visits and hospitalizations are encouraged be collected to further supplement these visits and the clinical information that is obtained about individual episodes of respiratory illness. Additionally, clinical information will be collected to evaluate the severity of the clinical case. All participants who report symptoms of RSV-like illness will receive eDiary prompts to complete the PRO questionnaires.
12. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry, but the information entered in the eDiary must come from the participant.
13. Participants can call the site at any time starting Day 15 after their injection to report any RSV-like illness/symptoms. If it is in between prompts the participant should not wait until the next prompt to report the symptoms. A site visit should be arranged for medical evaluation and to obtain a nasopharyngeal swab within 5 days, if possible, after symptom onset or worsening.
14. Participants who develop RSV-like illness and provide a nasopharyngeal swab specimen will be contacted weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or through 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications.
15. Nasopharyngeal swab samples will be tested for the presence of RSV, SARS-CoV-2, and other respiratory pathogens by RT-PCR. Data from specimens obtained at a healthcare visit external to the study or mobile site may be accepted.

16. Medically qualified study staff will contact all participants. The participant will be interviewed according to the script and information will be collected about occurrence of unsolicited AEs through 28 days post-vaccination, AESIs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations.
17. The Edmonton Frail Scale will be used to assess participant frailty status at baseline, 12 months, and 24 months. Responses will be recorded on the appropriate eCRF page.
18. All participants will receive eDiary prompts to complete the EQ-5D-5L questionnaire quarterly. For participants reporting symptoms of RSV-like illness, the EQ-5D-5L responses will be collected using the eDiary on the day that the symptoms start (up to 1 additional day), and at 4 days (± 1 day) and 14 days (± 1 day) after the start of the symptoms.
19. For participants reporting symptoms of RSV-like illness, the WPAI over the previous 7 days will be collected using the eDiary at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms.
20. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after the study injection; all concomitant medications relevant to or for the treatment of an AESI, SAE, or MAAE will be recorded from Screening through Day 730.
21. All hospitalizations, outpatient/physician visits and emergency room/urgent care visits associated with MAAEs or SAEs will be recorded from Day 1 through Day 730.

Table 22: Schedule of Events (Part B Substudy) (Select US Sites Only)

Visit Number		1		2		3	USIV
Type of Visit/Contact	V	V	SC	V[1]	SC	V	V
Month Timepoint	NA	NA	NA	M1	Up to M6	M6	Up to M6
Visit Day	Screening[2] (M24 post-primary dose)	BD D1[2] (Baseline)	BD D8	BD D29	BD D60 then every 60 days[3]	BD D181 /EOS	NA
Window Allowance (Days)	-90	+14 from Screening Visit	+3	+5	±14	±14	NA
Informed consent form	X						
Medical history, prior medications		X[4]					
Physical examination[5]	X	X					
Vital signs[6]	X	X					X
Confirmation of inclusion/ exclusion criteria[7]	X	X					
Unblinding of vaccination group assignment[8]	X						
Randomization		X					
Serum (Ab)		X[9]		X		X[10]	
BD study injection		X					

Visit Number		1		2		3	USIV
Type of Visit/Contact	V	V	SC	V[1]	SC	V	V
Month Timepoint	NA	NA	NA	M1	Up to M6	M6	Up to M6
Visit Day	Screening[2] (M24 post-primary dose)	BD D1[2] (Baseline)	BD D8	BD D29	BD D60 then every 60 days[3]	BD D181 /EOS	NA
Window Allowance (Days)	-90	+14 from Screening Visit	+3	+5	±14	±14	NA
eDiary activation for recording solicited ARs (7 days) and 60-minute post-injection solicited AR assessments, vital signs, and eDiary entry review		X[11]					
Review of eDiary for recording solicited ARs[12]			X				
RSV diagnostic test[13]							X
eDiary prompts to solicit symptoms of RSV-like illness[14]			Monthly eDiary prompts[15]				
Unscheduled visit (for RSV-like symptoms)							X
Passive surveillance[16]			X	X	X	X	
RSV symptom log[17]							X
Nasopharyngeal swab for virus detection[18]							X
Follow-up safety contact[19]			X		X		X[17]
Recording of unsolicited AEs		X	X	X			
Recording of MAAEs, AESIs, SAEs, or AEs leading to study withdrawal, hospitalizations or outpatient treatment-related to or for the treatment of the MAAE/AESI/SAE[20]		X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[21]	X	X	X	X	X	X	X
Substudy completion						X	

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse events of special interest; AR = adverse reaction; BD = booster dose; CLIA = Clinical Laboratory Improvement Amendment; eCRF = electronic case report form; eDiary = electronic diary; EOS = end of study; IM = intramuscular; IP = investigational product; M = month; MAAE = medically-attended adverse event; NA = not applicable; RSV = respiratory syncytial virus;

RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety contact; USIV = unscheduled illness visit; V = study visit.

1. All study visits, with the exception of the Screening and BD Day 1 visit(s), can take place at the study or mobile site or other off-site location including the participant's home, where allowed by local regulations. 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 BD Day 1.
2. Screening and BD Day 1 activities may be performed on the same day or on different days. However, BD Day 1 activities must occur within 14 days after Screening.
3. The safety contact should occur on Day 60 and then every 60 days thereafter, but if there is a scheduled visit performed in the month then no safety contact is needed in that month. If a safety contact cannot be made at a given timepoint, due to any reason, then the site should attempt to complete the safety contact at any other time within that calendar month. If the patient calls the site to report RSV-like symptoms, this phone call should be recorded as an unscheduled safety call.
4. Any new medications or medical conditions that start after the Month 24/EOS visit of Part A and before the Screening Visit of Part B will be collected.
5. A full physical examination, including height and weight (body mass index will be calculated), will be performed at the Screening visit, and symptom-directed physical examinations will be performed at other study visits, if clinically indicated. Interim physical examinations will be performed at the discretion of the investigator. On the day of study injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.
6. Vital signs measurements include assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturation. The preferred route of temperature assessment is oral. Fever is defined as a body temperature ≥ 37.8°C/100.0°F. The participant will be seated for at least 5 minutes before all measurements are taken. On BD Day 1, vital sign measurements will be collected once before the study injection and at least 60 minutes after the study injection (before participants are discharged from the study site). Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.
7. Confirm initial eligibility (ie, the participant meets all inclusion and exclusion criteria aside from Inclusion Criterion #5 [randomized to and subsequently received mRNA-1345]) before the participant's vaccination group assignment is unblinded to designated unblinded site staff. Participants who meet all eligibility criteria, including Inclusion Criterion #5, are eligible for Part B.
8. For participants who meet initial eligibility, vaccination group assignment will be unblinded to designated unblinded site staff.
9. Baseline immunogenicity sample must be collected prior to study injection.
10. In cases when EOS is the early termination visit, immunogenicity samples should be taken at this unscheduled visit.
11. On the day of study injection (BD Day 1), participants will be given eDiaries and trained to use them. Participants will record data into the eDiary starting approximately 60 minutes after injection under supervision of the study staff to ensure successful entry of assessments. See Section 4.6.2.2 for additional detail.
12. ARs recorded in the eDiary beyond Day 7 should be reviewed by the investigator either via telephone call or electronic means or at the following study visit, or during an unscheduled visit.
13. Sites should attempt to collect data from tests conducted for RSV illness if CLIA-certified and available to include in the eCRF when the testing is done outside the study site for the RSV illness.
14. The eDiary will be activated for collection of RSV-like symptoms or respiratory disease every month starting 14 days after the study injection and lasting until BD Day 181/EOS. The eDiary will provide monthly prompts (every 30 days) to elicit symptoms of RSV-like illness and exposure to individuals with known RSV. If symptoms or worsening symptoms occur, study staff will arrange an unscheduled visit with the participant. See Section 4.6.5.2 for additional detail.
15. If the participant is unable to complete the eDiary on their own, a caregiver can assist with data entry, but the information entered in the eDiary must come from the participant.
16. Participants can call the site at any time starting 14 days after study injection to report any RSV-like illness/symptoms. If it is in between eDiary prompts the participant should not wait until the next prompt to report the symptoms. A site visit should be arranged for medical evaluation and to obtain a nasopharyngeal swab within 5 days, if possible, after symptom onset or worsening.

17. Participants who develop RSV-like illness and provide a nasopharyngeal swab specimen will be contacted weekly via telephone calls or other electronic means/telecommunication through resolution (or return to baseline) of symptoms or through 30 days from the onset or worsening of RSV-like illness, whichever comes first. In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications.
18. Nasopharyngeal swab samples will be tested for the presence of RSV, SARS-CoV-2, and other respiratory pathogens by RT-PCR. Data from specimens obtained at a healthcare visit external to the study or mobile site may be accepted.
19. Medically qualified study staff will contact all participants. The participant will be interviewed according to the script and information will be collected about occurrence of unsolicited AEs through 28 days post-injection, AESIs, MAAEs, SAEs, or AEs leading to substudy withdrawal and concomitant medications associated with those events, and receipt of any nonstudy vaccinations.
20. All hospitalizations, outpatient/physician visits, and emergency room/urgent care visits associated with MAAEs or SAEs will be recorded from BD Day 1 through BD Day 181/EOS.
21. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after the study injection; all concomitant medications relevant to or for the treatment of an AESI, SAE, or MAAE will be recorded from Screening through BD Day 181/EOS.

6.2. APPENDIX 2: Study Governance Considerations

6.2.1. Regulatory and Ethical Considerations

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

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.

Applicable ICH GCP Guidelines.

Applicable laws and regulatory requirements.

The protocol, protocol amendments, ICF, Investigator Brochure, 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.

The investigator will be responsible for the following:

- 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 (if applicable), and all other applicable local regulations.

6.2.2. Study Monitoring

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

Determine the adequacy of the facilities.

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

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and Moderna in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB/IEC review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

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

Provide information and support to the investigator(s).

Confirm that facilities remain acceptable.

Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.

Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).

Record and report any protocol deviations not previously sent.

Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

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

In accordance with local regulations, investigators may convert study site visits to telemedicine visits with the approval of the Sponsor (Sections 3.6 and 4.6 for Procedures).

The DSMB will also have responsibility for safety monitoring in Part A of the study (Section 3.6.4.2).

6.2.3. Audits and Inspections

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

Authorized representatives of Moderna, a regulatory authority, and any IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6R2, and any applicable regulatory requirements. The investigator should contact Moderna immediately if contacted by a regulatory agency about an inspection.

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the participant

consent form and recruitment materials must be maintained by the investigator and made available for inspection.

6.2.4. Financial Disclosure

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

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

6.2.5. 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.

6.2.6. Informed Consent Process

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

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

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

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

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

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

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 14 days from the previous ICF signature date.

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

6.2.7. Protocol Amendments

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

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

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

6.2.8. Protocol Deviations

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

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

6.2.9. Data Protection

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

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

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

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

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

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

- 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.

6.2.10. Sample Retention and Future Biomedical Research

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

6.2.11. Data Quality Assurance and Quality Control

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

1. All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
2. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
3. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
4. Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study Monitoring Plan, Centralized Monitoring Plan, and Risk Management Plan.
5. The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
6. The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
7. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
8. Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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.

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

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

6.2.12. Data Collection and Management

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

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

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

AEs will be coded with the most current available version of MedDRA. Concomitant medications will be coded using the World Health Organization (WHO) – Drug Reference List.

6.2.13. Source Documents

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

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

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

6.2.14. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

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

6.2.15. Study and Site Closure

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

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

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

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

Continuation of the study represents a significant medical risk to participants.

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

Inadequate recruitment of participants by the investigator.

Discontinuation of further mRNA-1345 development.

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

6.2.16. Publication Policy

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

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

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

The clinical study plan and the results of the study will be published on publicly available clinical study registers. The results of and data from this study belong to Moderna.

6.3. APPENDIX 3: Adverse Events of Special Interest

Investigators should report all events that fall into the categories presented in Table 23 as an AESI per the reporting processes specified in Section 3.6.3.3. 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 23: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150×10^9 cells per liter • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
New onset of or worsening of the following neurologic diseases	Neurologic diseases include the following: • Guillain-Barré Syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per-protocol Section 3.6.3.3.1 • Follow the reporting procedures in protocol Section 3.6.3.10
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

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

Table 24: CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable Case**	**Confirmed Case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms[1]: • 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[1]: • 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
	AND ≥ 1 new finding of the following: • troponin level above upper limit of normal (any type of troponin) • abnormal ECG or EKG or rhythm monitoring findings consistent with myocarditis2 • abnormal cardiac function or wall motion abnormalities on echocardiogram -cMRI findings consistent with myocarditis[3]	**AND** ≥ 1 new finding of the following: • histopathologic confirmation of myocarditis[4] • cMRI findings consistent with myocarditis[3] 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.

Condition	Definition
Acute pericarditis[5]	Presence of ≥ 2 new or worsening of the following clinical features: • acute chest pain[6] • 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 patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; CDC = Center for Disease Control and Prevention; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

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

1. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
2. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of the following: 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.
3. Using either the original or the revised Lake Louise criteria: https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon.
4. 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.
5. Reference: https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon
6. 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 (Gargano et al 2021).

6.5. APPENDIX 5: SAE Contact Information for Reporting

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

Role	Name	mail /Fax
SAE Reporting (if eCRF is unavailable at time of SAE)	SAE Mailbox	Drugsafety@modernatx.com

6.6. APPENDIX 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Protocol Summary.

6.6.1. USA-1 Amendment to Amendment 2 (United States Country-Specific Amendment), 19 Sep 2023

This amendment is considered substantial because it significantly impacts the scientific value of the study.

Main Rationale for the Amendment:

The main rationale for Amendment 2-USA-1 is to include a booster substudy (Part B) to evaluate the safety, tolerability, and immunogenicity of a 50-µg booster dose of mRNA-1345 given approximately 24 months after a primary dose of mRNA-1345 (administered in Part A) in adults ≥ 60 years of age. The summary of changes table describes the changes made in Amendment 2-USA-1 relative to Amendment 2, including the sections modified and the corresponding rationales. The protocol was restructured in Amendment 2-USA-1. Section numbers in the summary of changes table reflect the updated section numbers. The synopsis of Amendment 2-USA-1 has been modified to correspond to changes in the body of the protocol. The List of Abbreviations and References were updated, as needed. Minor editorial or formatting changes are not included in the summary of changes table.

Summary of Major Changes in Protocol Amendment 2-USA-1

Section # and Name	Description of Change	Brief Rationale
Title Page and Protocol Approval – Sponsor Signatory Page	Updated medical monitor/sponsor signatory name and contact information.	Change in medical monitor/sponsor signatory.
1.1 Synopsis	Added Part B content. Labeled Part A content as such. Revised duration of Part A to account for possible early conduct of the Month 24 visit for Part B screening.	To add booster substudy (Part B).
1.2 Schema	Added study schema for Part B.	To add booster substudy (Part B).
2.1 Study Rationale	Added rationale for Part B.	To add booster substudy (Part B).
2.2 Background and Overview; 2.2.2 Clinical Studies	Updated section.	To include current epidemiological and clinical data.
2.3.1 Potential Benefits of Study Participation	Revised for Part B and to account for VE results from Part A.	To add booster substudy (Part B).
2.3.2 Risks from Study Participation and Their Mitigation	Updated with the Sponsor's current position on myo- and pericarditis.	To ensure participant safety.

Section # and Name	Description of Change	Brief Rationale
2.3.3 Overall Benefit/Risk Conclusion	Revised for Part B.	To add booster substudy (Part B).
3 Part A (including all subsections)	Added "Part A" to all headings and table and figure titles.	To distinguish Part A from Part B.
3.2.1 General Design (Part A)	Revised duration to account for possible early conduct of the Month 24 visit for Part B screening.	To add booster substudy (Part B).
3.4.2.8.1 Planned Unblinding (Part A)	Added by-participant unblinding at or shortly after the Month 24 visit for all participants.	To add booster substudy (Part B).
3.4.2.8.1 Planned Unblinding (Part A)	Added planned unblinding of participants after consenting to Part B participation and meeting initial eligibility criteria. Specified that participants who do not meet eligibility criteria will complete study activities in Part A according to the Part A SoE.	To add booster substudy (Part B).
3.6 Study Assessments and Procedures (Part A)	Added that for the subset of participants who consent to participation in Part B, conduct of the Month 24 visit up to 3 months (90 days) early is not a protocol deviation. Specified that participants who do not meet eligibility criteria will complete study activities in Part A according to the Part A SoE.	To add booster substudy (Part B).
3.6.1.3 Surveillance for RSV-Like Illness	Added adenovirus to list of pathogens for detection via nasopharyngeal swab.	To correct typo.
3.6.4.3 Independent Cardiac Event Adjudication Committee (Part A)	Updated with the Sponsor's current position on myo- and pericarditis.	To ensure participant safety.
4 Part B	Added a Phase 3 randomized, observer-blinded, placebo-controlled substudy of a booster dose (BD) of 50 µg mRNA-1345 administered approximately 24 months after a primary dose of mRNA-1345.	To evaluate the safety, tolerability, and immunogenicity of a BD of 50 µg of mRNA-1345 administered approximately 24 months after the primary dose.
6.1 Schedule of Events Table 20: Schedule of Events (Part A Phase 2 Segment); Table 21: Schedule of Events (Part A Phase 3 Segment)	Added to Footnote #1 that for the subset of participants who consent to participation in Part B, conduct of the Month 24 visit up to 3 months (90 days) early is not a protocol deviation.	To add booster substudy (Part B).

Section # and Name	Description of Change	Brief Rationale
6.1 Schedule of Events Table 22: Schedule of Events (Part B)	Added SoE for Part B.	To add booster substudy (Part B).
6.2.2 Study Monitoring	Clarified that the DSMB is only for Part A.	To add booster substudy (Part B).
6.5 Appendix 5: SAE Contact Information for Reporting	Removed fax number.	To provide current communication methods.

Abbreviations: DSMB = drug and safety monitoring board; VE = vaccine efficacy.

6.6.2. Global Amendment 2, 16 Nov 2022

Amendment 2, 16 Nov 2022

This amendment is considered to be substantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Main Rationale for the Amendment

The main rationale for this amendment is to harmonize the efficacy success criteria in this study with other RSV vaccine candidates.

Summary of Major Changes in Protocol Amendment 2

Section # and Name	Description of Change	Brief Rationale
3.4 Study Endpoint Definitions; 8.1.1 Efficacy Assessments Related to RSV Infection	Specified the number of symptoms for each RSV-LRTD endpoint	To differentiate between 2 separate endpoints
5.2 Exclusion Criteria	Added text to provide further explanation regarding immune-mediated disease	Participants with stable autoimmune diseases that do not require systemic immunosuppressants (per Exclusion Criteria #9) are permitted.
8.1.3 Surveillance for RSV-Like Illness; 8.3.2 Medically-Attended Adverse Events	Clarified text regarding MAAE reporting	To clarify that visits due to surveillance for RSV that would normally have not resulted in consultation of an HCP should not be reported as a MAAE.
8.4.2 Data and Safety Monitoring Board; 9.6.1 Interim Analyses	Modified text to state that the DSMB will review the interim analysis results and make recommendations to the Sponsor	To clarify the role of the DSMB in reviewing interim analysis results.

Section # and Name	Description of Change	Brief Rationale
9.6.1 Interim Analyses	The information fraction for performing the first IA was updated to 50% of planned RSV-LRTD cases (43 cases with ≥ 2 symptoms and 16 cases with ≥ 3 symptoms). The information fraction for performing the second IA was updated to 85% of planned RSV-LRTD cases (74 cases ≥ 2 symptoms and 28 cases with ≥ 3 symptoms). The threshold for performing the primary analysis was updated to 86 RSV-LTD cases with ≥ 2 symptoms and 32 RSV-LTD cases with ≥ 3 symptoms. The approximation spending function to preserve the type 1 error rate was changed to Pocock. Adjusted the LB for the VE alpha-adjusted CI for primary VE to 20%.	To harmonize the efficacy success criteria in this study with other RSV vaccine candidates.
11.1 Appendix 1: Schedule of Events	Visit numbers updated in Table 15	The visit numbers were updated to align with the original study visit numbering established by data management

Abbreviations: CI = confidence interval; DSMB = drug and safety monitoring board; IA = interim analysis; LB = lower bound; LRTI = lower respiratory tract infection; RSV-LRTD = respiratory syncytial virus (RSV)-induced lower respiratory tract disease (LRTD); SoC = Summary of Changes; VE = vaccine efficacy.

6.6.3. Global Amendment 1, 22 Sep 2022

Amendment 1, 22 Sep 2022: Current Amendment

This amendment is considered to be substantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Main Rationale for the Amendment

The main purpose of this amendment is to provide clarification and further details, where applicable, about several aspects of study conduct. The Summary of Changes table describes the changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. Minor editorial or formatting changes, including removal of redundant text or text not appropriate for the synopsis, are not included in this summary table.

Summary of Major Changes in Protocol Amendment 1

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, Protocol Amendment Summary of Changes, and Header	Updated the protocol version and date; added IRAS ID; updated name of Sponsor medical monitor to PPD.	Administrative updates.
Protocol Amendment Summary of Changes	Added Summary of Changes section.	To reflect amendment.

Section # and Name	Description of Change	Brief Rationale
1 Protocol Summary	Updated to reflect changes throughout the protocol.	Internal document consistency.
2.2.2 Clinical Studies; 4.3 Choice of Dose and Control Product	A rationale for the use of the 50-µg dose of mRNA-1345 was added.	Added for clarity.
3.1 Primary Objectives and Endpoints	The primary efficacy outcome is modified to include an RSV-LRTD 3 or more symptom definition to be tested in a hierarchical fashion after the RSV-LRTD 2 or more symptom definition.	To ensure the reliable capture of RSV-LRTD 3 or more symptom disease.
Section 1 Protocol Summary; 3 Objectives and Endpoints; and 9 Statistical Considerations	Defined primary endpoint language to state "RSV-LRTD with 2 or more symptoms" and "RSV-LRTD with 3 or more symptoms"; language has been updated appropriately to reflect this change in the appropriate sections (ie, Sections 1, 3, and 9).	To define and encompass the evaluable data effectively.
3.2.2 Other Secondary Objectives and Endpoints, 9.5.1.2 Analysis of Key Secondary and Other Secondary Efficacy Endpoints (for second entry only)	A secondary efficacy objective and associated endpoint was updated to evaluate first hospitalizations associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection. A secondary efficacy endpoint was updated to evaluate "vaccine efficacy to prevent a first episode of RSV-LRTD with 3 or more symptoms within a period of 14 days post-injection up to 24 months post-injection" AND a subsequent endpoint was added to evaluate "vaccine efficacy to prevent a first episode of RSV-LRTD with 2 or more symptoms within a period of 14 days post-injection up to 24 months post-injection." A secondary efficacy objective and associated endpoint was updated to evaluate first hospitalizations associated with	Each of these revisions was done to provide clinical clarity.

Section # and Name	Description of Change	Brief Rationale
	RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection. Evaluation of vaccine efficacy in the prevention of a first episode of all-cause LRTD was modified to include all episodes (ie, "first episode" is removed). Immunogenicity endpoints were modified by clarifying that analysis of serum RSV binding antibodies will be performed using geometric mean concentration and an analysis of seroresponse rate in RSV neutralizing antibodies was added.	
3.3 Exploratory Objectives	Evaluation of vaccine efficacy in the prevention or mitigation of RSV-LRTD and all-cause LRTD with at least 1, 2, 3 or, 4, or 5 symptoms was modified to at least 3 or 4 symptoms. Evaluation of vaccine efficacy in the prevention of a first episode of all-cause ARD up to 12 months post-injection, all-cause LRTD up to 24 months post-injection, and all-cause ARD up to 24 months post-injection were modified to include all episodes (ie, "first episode" was removed from each).	These revisions were done to provide clinical clarity.
3.3 Exploratory Objectives; 3.3.2 Linkage to Real-World Data; 4.1.1 Phase 2 Segment	Substudy for linking patient-level data to real-world electronic health databases specified as occurring at United States (US) sites only. Study design for Phase 2 occurred at US sites only.	This aspect of the study is currently only feasible in the US.
3.4 Study Endpoint Definitions; 8.1.1 Efficacy Assessments Related to RSV Infection; 8.1.2 Other Efficacy Assessments	The option was added to use radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection to confirm RSV-ARD, all-cause LRTD, and all-cause ARD. Additional minor revisions and reorganization was performed for clarity.	To align with allowing for the use of radiologic evidence in the RSV-LRTD definition.

Section # and Name	Description of Change	Brief Rationale
4.1 General Design	Names of countries participating or potentially participating in study phases were added. Moved text specific to monthly safety contacts and missed visits to Section 8 (and removed from synopsis).	Detail is added per requests from multiple sites to provide clarity on participating countries. Information appeared too detailed for synopsis and fit better in the Study Assessments and Procedures section.
4.1 General Design; 6.1 Investigational Product; Table 7 Investigational Products Administered	Updated information regarding mRNA-1345 dose, concentration, volume (vial and injected), appearance, and storage conditions.	To provide additional details regarding the study intervention.
4.1 General Design, 8.1.3 Surveillance for RSV-Like Illness	Clarified that the Day 15 visit is at the site in Phase 2 but can be a telephone visit in Phase 3. Clarified that active surveillance includes questions about exposure to individuals with known RSV. Added that worsening symptoms and/or RSV-like symptoms prior to the surveillance period should also result in scheduling of an unscheduled visit. Clarified that nasopharyngeal swab samples should still be collected even if outside of the preferred 5-day window (or if within 14 days after injection).	To reduce burden on sites and participants. For consistency with relevant data collected via the eDiary and eCRF. To ensure consistent assessment of participants throughout the study. To ensure that swab sample data are obtained.
4.1.1 Phase 2 Segment; 4.1.2 Phase 3 Segment; 9.3.1 Power Calculation for Primary Efficacy Endpoint; 9.6.1 Interim Analyses; Figure 1 Study Schema – Phase 2 Segment; Figure 2 Study Schema – Phase 3 Segment	The sample size is updated to expand to 37,000 participants and increase the power for the RSV-LRTD 3 or more symptom definition; 400 to 2,000 participants has been updated to approximately 2,000 participants in Phase 2; and 32,000 to 33,600 has been updated to approximately 35,000 in Phase 3. The “n” for the mRNA-1345 and placebo group has been revised to approximately 1,000 per group for Phase 2; the “n” for the mRNA-1345 and placebo group has been revised to approximately 17,500 per group for Phase 3.	Sample size increased to ensure that there is at least 90% power for the additional primary endpoint of RSV-LRTD with 3 or more symptoms.

Section # and Name	Description of Change	Brief Rationale
4.1.1 Phase 2 Segment	Table 5 was modified to include a more detailed breakdown of planned enrollment among age groups.	To provide details regarding target enrollment numbers for Phase 2.
4.1.2 Phase 3 Segment	Table 6 was modified to include a more detailed breakdown of planned enrollment among age groups. In Japan and South Korea, participants will only enter the Phase 3 segment of the study.	To provide details regarding target enrollment numbers for Phase 3. MFDS and PMDA require that Sponsor includes language providing this clarification.
4.2 Scientific Rationale for Study Design	Enrollment details were updated to allow for "most of" the participants to be enrolled during low levels of RSV activity or the historical start of RSV season and that enrollment may be reduced during the time of peak RSV season.	To allow for more flexibility in enrolling participants.
5.1 Inclusion Criteria	1. Revised to clarify that chronic medical diagnosis could include congestive heart failure (CHF) by replacing "specifically" with "including"; a link to chronic obstructive pulmonary disease (COPD) definitions was added.	Updated for clarity.
5.2 Exclusion Criteria	1. Updated to exclude those in another research study who received an investigational product within 6 months. 11: Added 100.0°F to correspond with 37.8°C.	1. Excludes potential participants that could affect the data integrity of the study. 11. To clarify and incorporate alternative temperature measurement.
6.1 Investigational Product	Corrected formulation information for the Phase 2 mRNA-1345 investigational product (IP); added specific information about the Phase 3 formulation; and added Table 7: Investigational Product Administered.	To provide accurate information.
6.1 Investigational Product; 6.2.4 Packaging and Labeling; 6.2.5 Storage	Added specific information about the Phase 3 formulation.	To provide updated information.

Section # and Name	Description of Change	Brief Rationale
6.2.1 Method of Randomly Assigning Participants to Vaccination Groups	Removed text describing how many participants were randomized in each phase.	Text was redundant with text in Sections 4.1.1 and 4.1.2 and did not provide useful details on methodology.
6.2.8 Blinding; 6.2.8.1 Planned Unblinding; 6.2.8.2 Unplanned Unblinding	New section (6.2.8) added to differentiate between blinding and unblinding; sections were reorganized.	Revised for clarity.
6.2.8.2 Unplanned Unblinding	Clarified requirements for investigator notification of Sponsor in the event of unblinding.	Revision per MHRA request.
6.3 Study Treatment Compliance; 8 Study Assessments and Procedures	Updated text on how to handle missing visits and moved from Section 6.3 to Section 8.	Modified to ensure that missed or delayed visits are not omitted and moved to a more appropriate location.
6.4.1 Prior Medications and Therapies	Specified that prior mRNA or COVID-19 vaccines should be recorded.	Revision per Data and Safety Monitoring Board (DSMB) request.
6.4.2 Concomitant Medications and Therapies	Removed text about antipyretics and analgesics taken prophylactically.	The text was redundant with a more detailed paragraph that was retained.
6.4.3 Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-protocol Analyses	Text added regarding influenza vaccine receipt. Removed text about prohibited drug therapy.	Revision per DSMB request. Revision per MHRA and PMDA request.
8 Study Assessments and Procedures	1. Clarified that unattended or delayed visits are considered protocol deviations but should still be completed. Clarified requirements for safety contacts. 2. Clarified that use of results from procedures conducted before the signing of the informed consent form (ICF) may be used for study purposes only if permitted by local regulations.	1. To ensure that missed or delayed visits are not omitted. 2. To ensure that any country-specific requirements for infectious disease screening are honored within the protocol.
8.1.1 Efficacy Assessments Related to RSV Infection, 8.1.2 Other Efficacy Assessments	Added text “in case of inability to fully assess other clinical parameters” from RSV-LRTD endpoint to RSV-ARD, all-cause LRTD, and all-cause ARD endpoints. Also, text for RSV-	Text was added and modified for clarity.

Section # and Name	Description of Change	Brief Rationale
	LRTD and RSV-ARD definitions reorganized.	
8.1.3 Surveillance for RSV-Like Illness	1. Definition of "Worsening" symptoms updated to include new or intensified respiratory symptoms. Clarified that site personnel are encouraged to obtain information from HCPs if the participant has an unscheduled, nonstudy site visit in response to episodes of respiratory disease. Data from specimens obtained using RSV diagnostic tests during these visits may be accepted; duration of symptoms and concomitant medications will be followed up. 2. Updated last paragraph of the section to include "All RT-PCR confirmed, symptomatic RSV-LRTI should be reported as MAAEs and if severe and/or an SAE, reported in an expedited time frame to the Sponsor." Removed "all confirmed cases of RSV will be captured as MAAEs (and as SAEs, if applicable), along with relevant concomitant medications and details about the severity, seriousness, and outcome. Inserted a cross-reference to Section 8.3.10: Reporting Adverse Events.	1. Updated for clarity. 2. Provided clarification for classifying RSV-LRTI as an MAAE.
8.2.2 Use of Electronic Diaries	Removed language related to safety surveillance and moved other text to Section 8.1.3.	Text was redundant with text in Section 8.1.3 and other text was moved there as it was a more appropriate location.
8.2.3 Demographics/Medical History	Race and ethnicity data are now collected.	Black and aboriginal race has been shown in some studies to be a risk factor for severe RSV disease; the reasons for potential racial disparities remain unclear but may relate to social factors. Birth in proximity to the RSV season, male gender, and exposure to tobacco smoke are additional factors that may increase the risk of

Section # and Name	Description of Change	Brief Rationale
		hospitalization following exposure to RSV.
8.2.4 Physical Examination; 11.1 Appendix 1: Schedule of Events	Removed "Any clinically significant finding identified during a study visit after the study injection should be reported as an Medically-attended adverse events (MAAE) from Section 8.2.4 and footnote 4 in Tables 14 and 15.	Text was inaccurate because a clinically significant finding may be either an MAAE or TEAE depending on the situation.
8.3.3 Adverse Events of Special Interest	Added hyperlink in Section 8.3.3 to include a cross-reference to Appendix 3 and serious adverse events (SAE) Hotline text removed.	To reference a list in Section 11.3 Appendix 3 that includes pertinent clinical information about AESIs. To highlight general reporting procedures for AESIs, the cross-reference to all AESIs is now included in this section.
8.3.5 Solicited Adverse Reactions	Corrected the temperature cutoff to define the solicited adverse reactions (AR) of fever.	Corrected to properly describe this parameter.
8.3.6 Recording and Follow-up of an adverse events (AE) and/or SAE; 8.3.8 Assessment of Intensity	Removed text related to ARs.	These sections relate to general safety information; ARs are covered elsewhere.
8.3.10 Reporting Adverse Events	Modified text to include applicable regulations outside of the US.	Revision per MHRA request.
8.3.10 Reporting Adverse Events; 11.5 APPENDIX 5: SAE Contact Information for Reporting	Updated contact information for reporting SAEs.	Contact information updated.
8.4.3 Independent Cardiac Event Adjudication Committee, APPENDIX 4: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines	Details for the independent Cardiac Event Adjudication Committee (CEAC) review committee were added.	To align with standardized protocol language and safety monitoring practices.
8.5. Management of Overdose	Added "Any dosing errors throughout the study will be reported as protocol deviations	To provide clarity on how overdoses will be managed and reported.

Section # and Name	Description of Change	Brief Rationale
	(Section 11.2.8). The HCP should be able to guide the participants for any additional treatment needed. The participant must be followed closely for safety."	
8.9.1.1 EFS	Details for the Edmonton Frail Scale (EFS) were added.	To provide this information previously excluded from the protocol.
9.1 Blinding and Responsibility for Analyses; 9.5 Statistical Analyses	Removed the futility analysis.	The futility analysis has been removed because study enrollment would have been nearly complete when the DSMB reviewed the futility analysis results; this is the result of a lower than projected RSV-LRTD case accrual rate.
9.2 Statistical Hypothesis 9.3.2 Power Calculation for the Key Secondary Efficacy Endpoints	Statistics hypothesis, power and sample size were modified.	To provide corresponding updates associated with the added primary endpoint for severe cases based on 3+ symptoms.
9.3.1 Power Calculation for Primary Efficacy Endpoint; 9.6.1 Interim Analysis	Added the qualifying term "at least" to precede 43 and 75 RSV-LRTD cases with 2 or more symptoms; also added to 16 and 28 RSV-LRT cases with 3 or more symptoms.	To allow for flexibility in minimum number of cases assessed in IA1 and IA2.
9.4. Analysis Populations	Revised language in mITT Set by removing "provide any RSV serology data and/or" and "active" so the first paragraph now states "All participants in the FAS who complete at least 1 visit or surveillance 14 days after the IP administration."	To clarify the analysis population description for mITT Set.
9.5 Statistical Analyses 9.5.1 Efficacy Analyses 9.5.1.1 Analysis of Primary Endpoints 9.5.1.2 Analysis of Key Secondary and Other Secondary Efficacy Endpoints;	1. Updated primary analysis method. 2. Updated analysis method to secondary endpoints related to all-cause cases. 3. Moved multiplicity to Section 9.6.2.	1. A standard and more robust method of time to event analysis applied as the primary analysis for Vaccine efficacy endpoints. 2. Negative binomial regression model applied for corresponding updates associated with VE endpoints by incorporating recurrent cases in the analysis.
9.6.1 Interim Analyses 9.6.2 Multiplicity	1. Interim analyses were modified. 2. Multiplicity hierarchical testing sequence was modified.	To provide corresponding updates associated with the added primary endpoint for severe cases based on 3+ symptoms. Provide clarity.

Section # and Name	Description of Change	Brief Rationale
	3. Figure 4 was added to illustrate the testing sequence of primary, key secondary, and secondary endpoints. 4. Removed 'primary' from sentence to now only include planned 12-month analysis or final analysis	
10 References	Added reference for an interim analysis data memo.	To reflect revisions made to the background section.
11.1 Appendix 1: Schedule of Events	Updates to schedules and notes for consistency with protocol text. For the Phase 3 schedule of events, it was clarified that sites should record the safety contact even if the participant calls the site.	To provide clarity and ensure internal document consistency. Information added to remind sites that calls initiated by participants need to be recorded as well.
11.2.5 Recruitment Strategy	Section title modified and new template text added.	To align the text with the current Moderna protocol template and comply with European Union Clinical Trials Regulation requirements.
11.2.9 Data Protection	New template text added.	To align the text with the current Moderna protocol template and comply with European Union Clinical Trials Regulation requirements.
11.2.10 Sample Retention and Future Biomedical Research	Updated section to include mucus samples and remove whole blood.	To provide clarification regarding use of samples for future exploratory research.
11.6 APPENDIX 6: Protocol Amendment History	Appendix added with summaries of prior protocol amendments.	To identify and provide a summary of other protocol amendments.
11.6.1 Amendment 4 (DEU-1); 11.6.3 Amendment 2 (KOR-2)	Appendix sections will remove the term "CX 023398".	Term is no longer used in CMC product descriptions.

Abbreviations: AESI = adverse event of special interest; AR = adverse reaction; ARD = acute respiratory disease; BMI = body mass index; CHF = chronic heart failure; CMC = Chemistry, Manufacturing and Controls; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; DSMB = Data Safety Monitoring Board; eCRF = electronic case report form; eDiary = electronic diary; EFS = Edmonton Frail Scale; HCP = healthcare provider; ICF = informed consent form; IP = investigational product; IRAS ID = Integrated Research Application System identification; LRTD = lower respiratory tract disease; MAAE = medically-attended adverse event; MFDS = Ministry of Food and Drug Safety; MHRA = Medicines and Healthcare products Regulatory Agency; mRNA = messenger ribonucleic acid; PMDA = Pharmaceuticals and Medical Devices Agency; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SAE = serious adverse event; TEAE = treatment-emergent adverse event; US = United States; VE = vaccine efficacy.

6.6.4. DEU-1 Amendment to Original Protocol (Germany Country-Specific Requirements), 08 Jul 2022

Country-specific requirements for Germany are as follows:

For the Phase 3 segment of the study, each participant will receive a single dose of study injection (50 µg mRNA-1345 or placebo) as a 0.5-mL IM injection on Day 1. The mRNA-1345 Drug Product is a white to off-white dispersion containing 0.10 mg/mL mRNA in SM-102 LNP in 20 mM Tromethamine (Tris), 2.2 mM acetate, 87 g/L sucrose, pH 7.5. The mRNA-1345 Drug Product (50 µg) is supplied as a single-dose liquid with 0.7 mL volume, ready-to-use solution for IM administration in a 2R vial with a rubber serum stopper and an aluminum seal with flip-off plastic cap. The mRNA-1345 injection utilized in the Phase 3 portion of mRNA-1345-P301 is stored for 12 months at -25°C to -15°C that includes up to 180 days of storage at 2°C to 8°C and 48 hours at 8°C to 25°C.

Exclusion criterion 8 was revised to: "Received or plans to receive any nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 28 days before or within 28 days after the Day 1 study injection. Nonstudy vaccination(s) should not be delayed."

6.6.5. JPN-1 Amendment to Original Protocol (Japan Country-Specific Requirements), 02 Jul 2022

Country-specific requirements for Japan are as follows:

The JPN-1 amendment removes the following statement previously found in Section 3.4.4.3: "If a participant takes a prohibited drug therapy, the investigator and the CRO's medical monitor will make a joint decision about continuing or withholding dosing from the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or the interpretation of data."

For a complete list of all AESIs in this study, including thrombocytopenia and new onset of or worsening of neurological diseases, the list may be found in Section 6.3. Appendix 3: Adverse Events of Special Interest within the protocol amendment.

Japan will only participate in the Phase 3 segment of the mRNA-1345-P301 study.

6.6.6. KOR-2 Amendment to Original Protocol (Korea Country-Specific Requirements), 28 Jun 2022

Country-specific requirements for South Korea are as follows:

South Korea will only participate in the Phase 3 segment of the study.

The mRNA-1345-P301 Phase 2/3 study does not contain early termination/suspension criteria. Study safety oversight is provided by an IST and an independent DSMB.

For the Phase 3 segment of the study, each participant will receive a single dose of study injection (50 µg mRNA-1345 or placebo) as a 0.5-mL IM injection on Day 1. The mRNA-1345 Drug Product is a white to off-white dispersion containing 0.10 mg/mL mRNA in SM-102 LNP in 20 mM Tromethamine (Tris), 2.2 mM acetate, 87 g/L sucrose, pH 7.5. The mRNA-1345 Drug

Product (50 µg) is supplied as a single dose liquid with 0.7 mL volume, ready-to-use solution for IM administration in a 2R vial with a rubber serum stopper and an aluminum seal with flip-off plastic cap. mRNA-1345 Injection utilized in the Phase 3 portion of mRNA-1345-P301 is stored for 12 months at -25°C to -15°C that includes up to 180 days of storage at 2°C to 8°C and 48 hours at 8°C to 25°C.

In the mRNA-1345-P301 Protocol dated 07 October 2021, an error was noted in the "Analysis of Primary Efficacy Endpoint" section of Section 1.1 Synopsis: The adjusted alpha was listed incorrectly because the value did not include the planned 2 interim analyses and 1 final analysis. The corrected amendment states that "The study will be considered to meet the primary efficacy objective if the lower bound of the 2-sided (1-adjusted alpha) × 100% Farrington and Manning score-based CI of VE rules out 30%, *the adjusted alpha at the IAs and primary analysis will be 0.08%, 1.46%, and 4.54%, respectively, with overall 2-sided alpha for the primary endpoint = 5%.*" Alpha values stated throughout the rest of the protocol align with this correction and will be applied to all planned primary efficacy endpoint analyses in the mRNA-1345-P301 study.

6.6.7. KOR-1 Amendment to Original Protocol (Korea Country-Specific Requirements), 09 Jun 2022

Country-specific requirements for South Korea are as follows:

Exclusion criterion 1 was revised as per Article 5 Paragraph 1 of Regulations on Approval for Investigational New Drug Application (Ministry of Food and Drug Safety [MFDS], Republic of Korea). The exclusion criterion was revised to exclude individuals who had participated in another clinical study within 6 months prior to the screening, to align with this local regulation.

6.6.8. GBR-1 Amendment to Original Protocol (Great Britain Country-Specific Amendment), 10 May 2022

Amendment GBR-1, 10 May 2022

This amendment is considered to be nonsubstantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Main Rationale for the Amendment:

The main purpose of this amendment is to implement requests by the Medicines and Healthcare Products Regulatory Agency. The summary of changes table describes the changes made in Amendment GBR-1 relative to the original protocol, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment GBR-1:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, Protocol Amendment Summary of Changes, and Header	Updated the protocol version and date; added IRAS ID; updated name of sponsor medical monitor.	Administrative updates.
Protocol Amendment Summary of Changes	Added summary of changes section.	To reflect amendment.
Section 6.2.8.2 Unplanned Unblinding	Clarified requirements for investigator notification of sponsor in the event of unblinding.	MHRA request.
Section 6.4.3 Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-protocol Analyses	Removed text about prohibited drug therapy.	MHRA request.
Section 8.3.10 Reporting Adverse Events	Modified text to include applicable regulations outside of the US.	MHRA request.

Abbreviations: GBR = Great Britain; IRAS ID = Integrated Research Application System identification; MHRA = Medicines and Healthcare products Regulatory Agency.

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