ModernaTX, Inc.

mRNA-1345-P301

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

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Statistical Analysis Plan

Version 2.0

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TABLE OF CONTENTS

1. INTRODUCTION 9

2. STUDY OBJECTIVES 9

2.1. PRIMARY OBJECTIVES 9
2.1.1. Primary Safety Objective 9
2.1.2. Primary Efficacy Objective 9
2.2. SECONDARY OBJECTIVES 10
2.2.1. Key Secondary Efficacy Objectives 10
2.2.2. Other Secondary Efficacy Objectives 10
2.2.3. Secondary Immunogenicity Objective 10
2.3. EXPLORATORY OBJECTIVES 11

3. STUDY ENDPOINTS 14

3.1. PRIMARY ENDPOINTS 14
3.1.1. Primary Safety Endpoints 14
3.1.2. Primary Efficacy Endpoints 14
3.2. SECONDARY ENDPOINTS 15
3.2.1. Key Secondary Efficacy Endpoints 15
3.2.2. Other Secondary Efficacy Endpoints 16
3.2.3. Secondary Immunogenicity Endpoints 17
3.3. EXPLORATORY ENDPOINTS 17

4. STUDY DESIGN 20

4.1. OVERALL STUDY DESIGN 20
4.2. STATISTICAL HYPOTHESIS 21
4.3. SAMPLE SIZE AND POWER 22
4.3.1. Power Calculation for Primary Efficacy Endpoint 22
4.3.2. Power Calculation for the Key Secondary Efficacy Endpoints 24
4.4. RANDOMIZATION 25
4.5. BLINDING AND UNBLINDING 25

5. ANALYSIS POPULATIONS 26

5.1. RANDOMIZATION SET 26
5.2. FULL ANALYSIS SET 26
5.3. MODIFIED INTENT-TO-TREAT SET 26
5.4. PER-PROTOCOL EFFICACY SET 27
5.5. PER-PROTOCOL IMMUNOGENICITY SET AND ANALYSIS POPULATION FOR IMMUNOGENICITY 27
5.6. SOLICITED SAFETY SET 28
5.7. SAFETY SET 28

6. STATISTICAL ANALYSIS 29

6.1. GENERAL CONSIDERATIONS 29
6.2. BACKGROUND CHARACTERISTICS 31

6.2.1. Participant Disposition ... *31*
6.2.2. Demographics and Baseline Characteristics ... *33*
6.2.3. Medical History ... *33*
6.2.4. Prior and Concomitant Medications ... *34*
6.2.5. Concomitant Procedures/Surgeries ... *35*
6.2.6. Significant Protocol Deviations ... *36*
6.2.7. COVID-19 Impact ... *36*
6.3. EFFICACY ANALYSIS ... 36
6.3.1. Analysis of the Primary Efficacy Endpoints ... *37*
6.3.1.1. Primary Efficacy Endpoints Primary Definition/Derivation ... 37
6.3.1.2. Primary Efficacy Endpoints Alternative Definition/Derivation ... 39
6.3.1.3. Primary Analysis Approach ... 39
6.3.1.4. Sensitivity Analysis ... 41
6.3.1.5. Supportive Analysis ... 42
6.3.1.6. Subgroup Analysis ... 43
6.3.2. Analysis of the Secondary Efficacy Endpoints ... *44*
6.3.2.1. Derivation of Cases for Key Secondary Efficacy Endpoints ... 44
6.3.2.2. Analysis of the Key Secondary Efficacy Endpoints ... 46
6.3.2.3. Derivation of Cases and Endpoints for Other Secondary Efficacy Endpoints ... 47
6.3.2.4. Analysis of Secondary Efficacy Endpoints ... 50
6.3.3. Analysis of Exploratory Efficacy Endpoints ... *53*
6.4. PLANNED ANALYSES ... 57
6.5. MULTIPLICITY ADJUSTMENT ... 60
6.6. SAFETY ANALYSIS ... 63
6.6.1. Solicited Adverse Reactions ... *63*
6.6.2. Unsolicited Treatment-emergent Adverse Events ... *65*
6.6.2.1. Overview of Unsolicited TEAEs ... 67
6.6.2.2. TEAEs by System Organ Class and Preferred Term ... 68
6.6.2.3. TEAEs by Preferred Term ... 69
6.6.2.4. TEAEs by Severity ... 69
6.6.2.5. TEAEs by System Organ Class, High Level Group Term, and Preferred Term 69
6.6.2.6. Independent Cardiac Event Adjudication Committee ... 69
6.6.2.7. Subgroup Analysis of TEAEs ... 70
6.6.3. Vital Sign Measurements ... *70*
6.7. IMMUNOGENICITY ANALYSIS ... 71
6.7.1. Sampling of the Immunogenicity Subset (Case-Cohort Sampling Design) ... *72*
6.7.2. Analysis Set for Immunogenicity Analysis ... *72*
6.7.3. Immunogenicity Data ... *72*
6.7.4. Summary of Antibody-Mediated Immunogenicity Endpoints ... *72*
6.7.5. Subgroup Analysis ... *73*
6.8. DATA SAFETY MONITORING BOARD ... 74
7. CHANGES FROM PLANNED ANALYSES IN PROTOCOL ... 74
8. REFERENCES ... 75
9. LIST OF APPENDICES ... 77

9.1. APPENDIX A STANDARDS FOR VARIABLE DISPLAY IN TABLES, FIGURES AND LISTINGS (TFLS) 77
9.2. APPENDIX B ANALYSIS VISIT WINDOWS 78
9.3. APPENDIX C IMPUTATION RULES FOR MISSING DATES OF PRIOR/CONCOMITANT MEDICATIONS 78
9.4. APPENDIX D IMPUTATION RULES FOR MISSING DATES OF AES 79
9.5. APPENDIX E IMPUTATION RULES FOR MISSING DATES OF PROCEDURES/SURGERIES 80
9.6. APPENDIX F WORLD BANK REGIONS AND INCOME CLASSIFICATIONS 80
9.7. APPENDIX G SCHEDULE OF EVENTS 82
9.8. APPENDIX H ESTIMANDS AND ESTIMAND SPECIFICATIONS 92
9.9. APPENDIX I ADVERSE EVENTS OF SPECIAL INTEREST 99
9.10. APPENDIX J DEFINITION OF TEAE OF SPECIAL INTEREST BY SMQ 100
9.11. APPENDIX K MEDICAL CONDITIONS OR ADVERSE EVENTS BY SOC/HLGT/PT 103

DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	29NOV2022	Final version
2.0	31MAY2023	1. Added new exploratory efficacy objectives and endpoints in Section 2.3, 3.3 and 6.3.3 regarding: • the VE in the prevention of the first episode of RSV-LRTD with shortness of breath and at least one other LRTD symptom as compared with placebo within the period of 14 days post-injection up to 12 months post-injection, and within the period of 14 days post-injection up to 24 months post-injection. • the VE in the prevention of the first episode of RSV-LRTD with hypoxemia and tachypnea as two symptoms of lower respiratory tract involvement as compared with placebo within the period of 14 days post-injection up to 12 months post-injection, and within the period of 14 days post-injection up to 24 months post-injection. • the VE in the prevention of the first hospitalization associated with an RSV positive case as compared with placebo within the period of 14 days post-injection up to 24 months post-injection, and within the period of 14 days post-injection up to 24 months post-injection. • the VE in the prevention of the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 24 months post-injection, and within the period of 14 days post-injection up to 24 months post-injection. 2. Added the definition of case duration for RSV-LRTD in Section 6.3.1 3. Added new sensitivity analysis of excluding co-infection of any other non-RSV pathogen in Section 6.3.1.4 and 6.3.2. 4. Added summary of TEAEs with rate difference and the corresponding 95% CI using Miettinen Nurminen method, for PTs reported by at least 0.1% of participants in any vaccination group in Section 6.6.2.

		5. Added Summaries of CEAC adjudication outcomes in Section 6.6.2 6. Updated the review process of the targeted medical history data in Section 6.2.3. 7. Added analyses of medical history and TEAEs based on selected HLGTs, AESIs in response to agency requests in Section 6.2.3 and Section 6.6.2. 8. Updated analyses of SMQs in response to agency request in Section 6.6.2. 9. Updated subgroup analysis for solicited adverse reactions in Section 6.6.1 and unsolicited treatment-emergent adverse events in Section 6.6.2

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
ARD	acute respiratory disease
ATC	Anatomical Therapeutic Chemical
bAb	binding antibodies
BMI	body mass index
ccIAS	case-cohort Immunogenicity Analysis Set
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSP	clinical study protocol
DBP	data blinding plan
DSMB	data safety monitoring board
eCRF	electronic case report form
eDiary	electronic diary
EFS	Edmonton Frailty Scale
FAS	full analysis set
GLSM	geometric least squares mean
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold-rise
GMR	geometric mean titer ratio
GMT	geometric mean titer
IA	interim analysis
IcEv	intercurrent event
IM	intramuscular
IP	investigational product
IRT	Interactive Response Technology
LLOQ	lower limit of quantification
LRTD	lower respiratory tract disease
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	mixed model for repeated measures
MTP	multiple testing procedure
nAb	neutralizing antibodies
NP	nasopharyngeal

PPE	per-protocol efficacy
PPI	per-protocol immunogenicity
PRO	Patient-Reported Outcome
PT	preferred term
QoL	quality of life
RCDF	reverse cumulative distribution function
RSV	Respiratory Syncytial Virus
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SMQ	Standardised MedDRA Queries
SOC	system organ class
SoEs	Schedules of Events
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
TFLs	Tables, Figures and Listings
ULOQ	upper limit of quantification
VE	vaccine efficacy
WHO-DD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Introduction

This statistical analysis plan (SAP), version 2.0, is based on clinical study protocol (CSP) amendment 2, dated 16-November-2022 and the approved electronic case report form (eCRF) Version 13.005, dated 14-November-2022.

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

Study mRNA-1345-P301 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 targeting Respiratory Syncytial Virus (RSV) in adults $\geqslant$ 60 years of age as compared with placebo.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis; Statistical Analysis System (SAS) Version 9.4 or higher will be used.

In this document, IP injection, injection and dose are used interchangeably.

2. Study Objectives

2.1. Primary Objectives

2.1.1. Primary Safety Objective

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

2.1.2. Primary Efficacy Objective

The primary efficacy objective is to evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the 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.

2.2. Secondary Objectives

2.2.1. Key Secondary Efficacy Objectives

The key secondary efficacy objectives are:

- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-associated acute respiratory disease (RSV-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 the 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.

2.2.2. Other Secondary Efficacy Objectives

The other secondary efficacy objectives are:

- 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.
- 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.
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-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 the first episode of RSV-LRTD as compared with placebo by RSV subtype.
- To evaluate the efficacy of a single dose of mRNA1345 vaccine in the prevention of the 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.
- 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.

2.2.3. Secondary Immunogenicity Objective

The secondary immunogenicity objective is to evaluate the response to a single dose of mRNA-1345 vaccine from baseline up to 24 months post-injection.

2.3.Exploratory Objectives

The exploratory objectives 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.

  As part of this objective, the following combinations will be also described:
  - To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD with shortness of breath and at least one other symptom of lower respiratory tract involvement 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 the first episode of RSV-LRTD with hypoxemia and tachypnea as two symptoms of lower respiratory tract involvement 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 the first episode of RSV-LRTD with shortness of breath and at least one other symptom of lower respiratory tract involvement 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 the first episode of RSV-LRTD with hypoxemia and tachypnea as two symptoms of lower respiratory tract involvement 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 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 the 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 the 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 the 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 the 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 five 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).
- To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first hospitalization associated with an RSV positive case 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 the first hospitalization associated with an RSV positive case 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 the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen 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 the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.

3. Study Endpoints

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

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

- 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 AEs (MAAEs) up to 24 months post-injection.
- AEs of Special Interest (AESIs) up to 24 months post-injection.
- Serious AEs (SAEs) up to 24 months post-injection.
- AEs leading to study withdrawal up to 24 months post-injection.

3.1.2. Primary Efficacy Endpoints

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

- Vaccine efficacy (VE) of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.

RSV-LRTD with 2 or more symptoms is defined based on the following criteria:

- The participant must have a nasopharyngeal swab which tests positive for RSV infection by reverse transcription polymerase chain reaction (RT-PCR)

  AND

- The participant must have experienced 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 the case definition of "RSV-LRTD with 2 or more symptoms".

RSV-LRTD with 3 or more symptoms is defined based on the following criteria:

- The participant must have a nasopharyngeal swab which tests positive for RSV infection by RT-PCR

  AND

- The participant must have experienced 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 the case definition of "RSV-LRTD with 3 or more symptoms".

3.2. Secondary Endpoints

3.2.1. Key Secondary Efficacy Endpoints

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

- VE of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

RSV-ARD is defined as an acute symptomatic respiratory disease based on the following criteria:

- The participant must have a nasopharyngeal swab which tests positive for RSV infection by RT-PCR

  AND

- The participant must have experienced new or worsening of at least ONE of the following symptoms: 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 the case definition of " RSV-ARD".

3.2.2. Other Secondary Efficacy Endpoints

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

- VE of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection
- VE of mRNA-1345 to prevent all-cause LRTD (all-cause LRTD is referring to 2 or more symptoms onwards) within the period of 14 days post-injection up to 12 months post-injection
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection based on RSV subtype A positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection based on RSV subtype B positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection based on RSV subtype A positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection based on RSV subtype B positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection based on RSV subtype A positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection based on RSV subtype B positive cases.
- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection based on RSV subtype A positive cases.

- VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection based on RSV subtype B positive cases.
- VE of mRNA-1345 to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection.
- Change in total frailty score from baseline to 12 months and 24 months post-injection, using the Edmonton Frail Scale (EFS).

3.2.3. Secondary Immunogenicity Endpoints

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

- Geometric mean titer (GMT) of serum RSV neutralizing antibodies (nAbs) and geometric mean concentration (GMC) of serum RSV binding antibodies (bAbs) at baseline (Day 1), Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546 and Day 730.
- Seroresponse rate (SRR) of serum RSV nAbs and bAbs at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546 and Day 730. Seroresponse for RSV nAbs is defined as:
    - a post-injection titer ≥ 4 x lower limit of quantification (LLOQ) if baseline is < LLOQ

      OR
    - a ≥ 4-fold increase from baseline in post-injection titers if baseline is ≥ LLOQ.
- Geometric mean fold rise (GMFR) of post-injection/baseline titers for RSV nAbs and bAbs at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546 and Day 730.
- Proportion of participants with ≥ 2-fold increases in RSV nAb titers and bAb concentration at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546 and Day 730.

3.3. Exploratory Endpoints

The exploratory objectives will be evaluated by the following endpoints:

- Immune response biomarkers after dosing with mRNA-1345 vaccine as potential correlates of protection or risk of RSV disease.
- 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.
- VE of mRNA-1345 to prevent or mitigate RSV-LRTD and all-cause LRTD with at least 1, 2, 3, 4, or 5 symptoms or signs of lower respiratory tract involvement.

  - VE of mRNA-1345 to prevent - the first episode of RSV-LRTD with shortness of breath and at least one other symptom of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection.
  - VE of mRNA-1345 to prevent the first episode of RSV-LRTD with hypoxemia and tachypnea as two symptoms of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection.
  - VE of mRNA-1345 to prevent - the first episode of RSV-LRTD with shortness of breath and at least one other symptom of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection.
  - VE of mRNA-1345 to prevent the first episode of RSV-LRTD with hypoxemia and tachypnea as two symptoms of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection.VE of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 24 months post-injection.

- VE of mRNA-1345 to prevent all-cause ARD within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent all-cause LRTD within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent all-cause ARD within the period of 14 days post-injection up to 24 months post-injection.
- Number of participants in each baseline and subsequent worst living situation.
- VE of mRNA-1345 to prevent exacerbations of CHF up to 12 months and 24 months post-injection.
- VE of mRNA-1345 to prevent exacerbations of COPD up to 12 months and 24 months post-injection.
- Number of participants with the first episode of RSV-LRTD by baseline frailty status.
- Number of participants with the first episode of RSV-ARD by baseline frailty status.
- Number of participants with the 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.
- Number of participants with the 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.

- Number of deaths from all causes at 12 months and 24 months post-injection.
- Change from baseline in health-related quality of life (HRQoL) using the 5 level EuroQol 5 Dimension (EQ-5D-5L) utility index scores at 12 months and 24 months.
- Change from baseline in HRQoL for participants with RSV-LRTD or RSV-ARD using the EQ-5D-5L utility index scores at 12 months and 24 months
- 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 at the start of the symptoms (baseline), and at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms.
- Healthcare-related endpoints:
    - Number of participants with 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
    - Number of participants with new 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 encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes (US sites only).
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.

4. Study Design

4.1. Overall Study Design

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 Data Safety Monitoring Board (DSMB). Phase 2 will be conducted in the US only. The Phase 3 segment is a multinational trial 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 vaccination), 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. The Schedules of Events (SoEs) for the Phase 2 and Phase 3 segments of the study are given in Appendix G Table 9 and Table 10, respectively.

Each participant will receive a single dose of study injection (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 RSV-like illness symptoms or worsening symptoms are reported, the 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 the 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 treatment 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 non-study vaccinations.

4.2. Statistical Hypothesis

There are 2 primary efficacy objectives in this study, which will be tested in a hierarchical order, as stated in Section 6.5.

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 $\leqslant$ 20% (i.e., H^1_0: VE $\leqslant$ 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) $\geqslant$ 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 $\leqslant$ 20% (i.e., H^2_0: VE $\leqslant$ 20%). Equivalently, the null hypothesis is: H^2_0: hazard ratio (HR) $\geqslant$ 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.

4.3. Sample Size and Power

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.

4.3.1. Power Calculation for Primary Efficacy Endpoint

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, i.e., rejecting the null hypothesis H^1_0: VE $\leqslant$ 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 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 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, i.e., rejecting the null hypothesis H^2_0: VE $\leqslant$ 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:

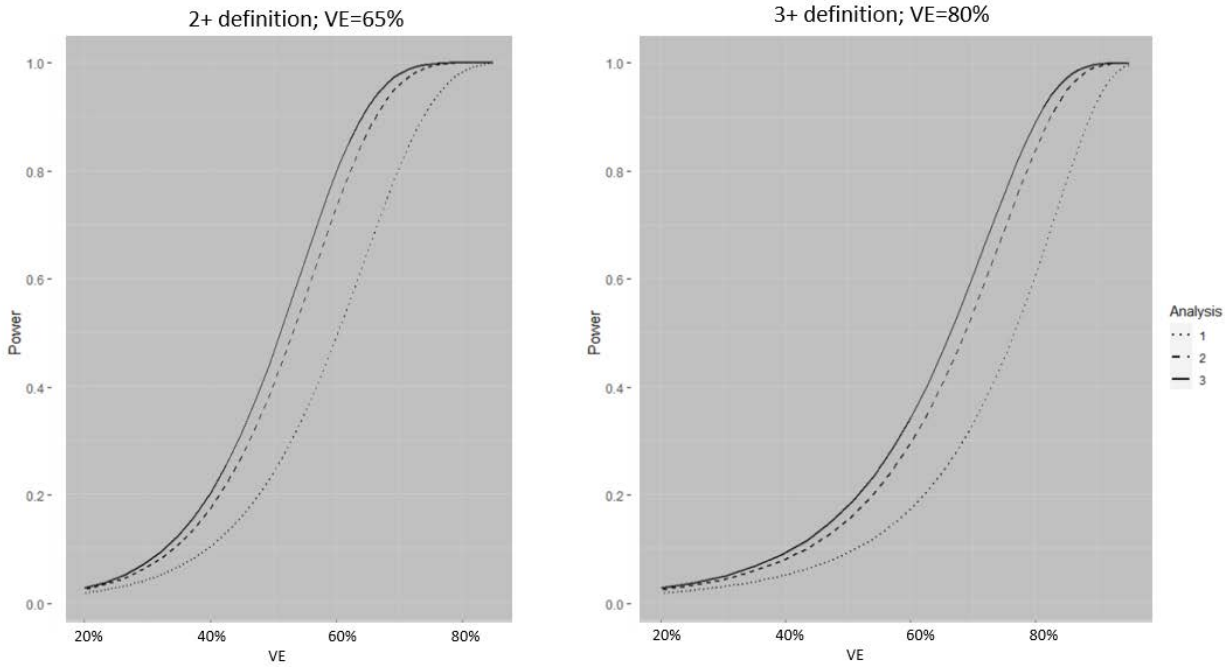
- The target VE against protocol-defined RSV-LRTD with 3 or more symptoms is 80%.
- An attack rate of 0.2% in the placebo arm for the protocol-defined RSV-LRTD with 3 or more symptoms.
- Two IAs at approximately 50% and 85% of total target RSV-LRTD cases with 3 or more symptoms across the 2 study vaccination 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 IA 1 for both primary endpoints will be conducted at the same time, i.e, IA 1 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, IA 2 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 1 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 1: Power of the Primary Efficacy Endpoints by Effect Size



Abbreviations: VE = vaccine efficacy; 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.

4.3.2. Power Calculation for the Key Secondary Efficacy Endpoints

For the key secondary endpoints, with approximately 18,500 participants per group, Table 1 and Table 2 provide power of demonstrating VE based on an attack rate of 2.0% for the first episode of RSV-ARD and a rate of 0.2% for the 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 the 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 the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

Table 1: Power of Demonstrating Vaccine Efficacy to Prevent the First Episode of RSV-ARD

True VE	Placebo Attack Rate	VE to Prevent the 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 2: Power of Demonstrating Vaccine Efficacy to Prevent the First Hospitalization Associated with RSV-ARD or RSV-LRTD

True VE	Placebo Hospitalization Rate	VE to Prevent the First Hospitalization 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.

4.4. Randomization

In both Phase 2 and Phase 3 segments of the study, assignment to vaccination groups will be stratified by age (60 to 74 years vs. ≥ 75 years) and risk factors for LRTD (present versus absent). The study will target enrollment of approximately 60% of participants 60 to 69 years of age, 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.

The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules.

4.5. Blinding and Unblinding

The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product (IP) administered until study end, with the certain exceptions specified in Section 6.2.8 of the protocol. More details of blinding and unblinding processes are specified in the study data blinding plan.

Confidential

Planned interim and primary analyses are described in Section 6.4 of this SAP and Section 9.6 of the protocol. 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 results of the IAs, provided by the independent unblinded statistician. Limited additional Sponsor personnel may be unblinded to the results of the IAs, if needed. The extent to which individuals are unblinded with respect to results of the planned IAs will be documented in the study data blinding plan. 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.

5. Analysis Populations

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

5.1. Randomization Set

The Randomization Set consists of 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.

5.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized participants who receive any IP. Participants will be analyzed according to the vaccination group to which they are randomized.

5.3. Modified Intent-to-Treat Set

The modified Intent-to-Treat (mITT) Set consists of 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 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.

5.4. Per-protocol Efficacy Set

The Per-Protocol Efficacy (PPE) Set consists of 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.

5.5. Per-Protocol Immunogenicity Set and Analysis Population for Immunogenicity

For characterizing immunogenicity of the vaccine, and for assessing correlates of risk and protection, a case-cohort sampling design will be used for measuring neutralizing antibodies (nAb) and binding antibodies (bAb) data from a selected subset of trial participants. This subset is referred as the case-cohort Immunogenicity Analysis Set (ccIAS). The ccIAS consists of a stratified random sample of trial participants (Random SubCohort), augmented with a subset of all participants with any post-injection RSV-ARD cases defined with eligible RSV-ARD symptoms and positive RT-PCR post injection (refer to Table 4 in Section 6.3.2.1). The immunogenicity samples of the ccIAS will be processed and the immunogenicity data will be available for the ccIAS. Refer to Immunogenicity sampling plan for the details of ccIAS and Random SubCohort.

The Immunogenicity Subset consists of all participants in the ccIAS who had a valid baseline immunogenicity tier result (prior to the IP injection) and at least one valid post-baseline result.

The Per-Protocol Immunogenicity (PPI) Set will be used as the analysis population to characterize immunogenicity of mRNA-1345. The PPI set contains a randomly selected subset of participants (i.e. participants in the Random Subcohort) who

a) receive the assigned IP dose according to protocol, and
b) have RSV immunogenicity titer results at baseline (prior to the IP administration) and at least 1 valid result after the IP administration at timepoint of interest, and

c) have no major protocol deviation affecting the primary immunogenicity outcomes as determined prior to database lock and unblinding.

The analysis of characterizing immunogenicity of mRNA-1345 is included in Section 6.7, the primary analysis population to characterize immunogenicity of mRNA-1345 is the PPI Set (Section 6.7.2); the analysis of assessing correlates of risk and protection will be included in a separate Immune Correlates analysis plan. Participants will be analyzed according to the vaccination group to which they are randomized.

5.6. Solicited Safety Set

The Solicited Safety Set consists of all randomized participants who receive any IP and contribute any solicited ARs 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.

5.7. Safety Set

The Safety Set consists of 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.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Events is provided in the Appendix G in Tables 9 and 10.

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

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

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the date/time of IP injection. For immunogenicity endpoints, baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the date of IP injection.

Study day will be calculated as below:

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

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

For GMT/GMC calculations, antibody values reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ, unless otherwise specified. Missing results will not be imputed.

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

- In scheduled visit windows per specified visit windowing rules.

- In the derivation of baseline measurements.
- In the derivation of maximum/minimum values after dose and maximum/minimum change from baseline values for safety analyses.
- In individual participant data listings as appropriate.

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

Incomplete/missing data:

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

Vaccination groups

The following vaccination groups will be used for summary purposes:

- mRNA-1345 50 μg
- Placebo

If a participant received any dose of mRNA-1345, regardless of the group the participant is randomized to, the participant will be included to mRNA-1345 50 μg group as the actual vaccination group received for safety and reactogenicity analyses.

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

Analysis Periods

The following analysis periods and vaccination groups will be used for efficacy analyses:

Vaccination Group	Description	Analysis Period for Efficacy

mRNA-1345 50 µg	Participants randomized to mRNA-1345 50 µg	From randomization to the earlier date of study discontinuation, study completion, death, or data cutoff date for efficacy
Placebo	Participants randomized to Placebo	

The analysis period and vaccination groups for Safety analyses is summarized below:

Vaccination Group	Description	Analysis Period for Safety
mRNA-1345 50 µg	Participants received mRNA-1345	From the dose of study IP to the earlier date of (study discontinuation, study completion, death, data cutoff date for safety)
Placebo	Participants received Placebo	

The above analysis period will be used to summarize unsolicited TEAEs throughout the study. The period up to 7 days after injection, that starts at the day of injection and continues through 6 subsequent days, will be used for analyses of solicited ARs. The period up to 28 days after injection, that starts at the day of injection and continues through 27 subsequent days, will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

6.2. Background Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following categories (analysis sets defined in Section 5) will be summarized as defined in Section 6.1 based on Randomization Set:

- Randomization Set
- Full Analysis Set
- Modified Intent-to-Treat Set
- Per-protocol Efficacy Set
- Per-Protocol Immunogenicity Set
- Solicited Safety Set

- Safety Set

The denominators of the percentages will be based on participants in the Randomization Set.

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

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

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

A separate summary table will include the number and percentage of randomized participants by vaccination group and overall with respect to each of the following groups: by country and site, by stratification factor at randomization (i.e. 60 to 74 years and at risk, 60 to 74 years and not at risk, $\geqslant$ 75 years and at risk, or $\geqslant$ 75 years and not at risk), by each of the two stratification factors at randomization separately (60 to 74 years vs. $\geqslant$ 75 years; at risk vs. not at risk) and by stratification factor derived from data collected on eCRFs (i.e. 60 to 74 years and at risk, 60 to 74 years and not at risk, $\geqslant$ 75 years and at risk, or $\geqslant$ 75 years and not at risk).

A concordance table of the number and percentage of patients in IRT randomization stratum and actual stratum derived from eCRF will be summarized by vaccination group based on the Randomization Set.

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

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

Participants with any inclusion and exclusion criteria violation will be provided in a listing.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2), Edmonton Frail Scale total score. The number and percentage of participants will be provided for categorical variables such as age group (actual age stratum derived from eCRF; and $\geqslant$ 60 and < 70 years, $\geqslant$ 70 and < 80 years, $\geqslant$ 80 years), comorbidities of interest (0 and $\geqslant$ 1 pre-existing comorbidities of interest including COPD, asthma, any chronic respiratory disease, any pulmonary disease, diabetes mellitus type 1 or 2, congestive heart failure, advanced liver disease or advance renal disease), sex, race, race group, ethnicity, actual LRTD risk factors (CHF/COPD present, CHF/COPD absent), BMI group, Edmonton Frail Scale total score category (0-3: Fit, 4-5: Vulnerable, 6-7: Mild Frailty, 8-9: Moderate Frailty, 10 or more: Severe Frailty), frailty status (Edmonton Frail Scale total score 0-3: Fit, 4-5: Vulnerable, 6 or more: Frail), world bank region, world bank income level 2022, History of COVID-19, and Hospitalization due to COVID-19 at baseline. Note that the comorbidities of interest and the actual LRTD risk factors will be derived using the targeted medical history data reviewed by blinded Moderna physicians as described in Section 6.2.3.

The summaries will be provided separately based on the Randomization Set, FAS, Safety Set, mITT Set, PPE Set and PPI Set.

6.2.3. Medical History

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

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1345 and then alphabetically within SOC. Number of events and number of participants with selected medical conditions, as indicated in Appendix K, will also be summarized by SOC, HLGT, and PT. Medical history data will be coded by SOC, HLGT, and PT according to the MedDRA Version 25.0.

Targeted medical history including COPD, asthma, any chronic respiratory disease (other than COPD or asthma), any pulmonary disease (other than COPD or asthma), diabetes mellitus type

1, diabetes mellitus type 2, congestive heart failure, advanced liver disease, advanced renal disease, other immune disease, COVID-19, other confirmed infectious respiratory illness requiring hospitalization, other confirmed non-infectious respiratory illness requiring hospitalization or unconfirmed respiratory illness requiring hospitalization and of participants hospitalized due to any respiratory illness and due to COVID-19 will be collected in the "Targeted Medical History" eCRF. A blinded review of the collected targeted medical history data will be performed periodically during the study by Moderna blinded physicians, to reassign the targeted medical history condition to the correct medical history category based on clinical judgement. The number and percentage of participants with any of the targeted medical history conditions will be provided using the clinical reviewed data. Similarly, the number and percentage of participants with these conditions which were ongoing at study entry will also be provided.

6.2.4. Prior and Concomitant Medications

Prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent will be recorded in the participant's eCRF. Prior mRNA or COVID-19 vaccines at any time in the participant's medical history will also be recorded. Medications and non-study vaccinations taken/received by the participant during the study will be recorded in the eCRF for the information as specified in Section 6.4.2 of the study protocol. Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHO-DD). The summary of medications will be based on the Safety set. Imputation rules for missing/partial dates for medications is detailed in Appendix C.

For analysis purpose, a medication prior to the IP injection date, regardless of whether the end date is before or after the IP injection, is defined "prior"; if the medication is taken between the IP injection date and up to 28 days after the IP injection (inclusive), then it is considered "concomitant", regardless of whether the start date is before or after the IP injection date; if the medication is taken after 28 days post IP injection (i.e. end date of the medication is after 28 days post IP injection OR ongoing after 28 days after IP injection), it is a "post" medication.

An overall summary of concomitant medications including the number and percentage of participants who take the following will be presented by vaccination group:

- Any concomitant medications and non-study vaccinations within 7 days post injection
- Any concomitant medications and non-study vaccinations within 28 days post injection
- Any non-study vaccinations within 7 days post injection
- Any non-study vaccinations within 28 days post injection
- Seasonal influenza vaccine within 28 days post injection
- Prophylactic antipyretics or analgesics medication within 28 days post injection
- Antipyretic or analgesic medication within 28 days post injection

The number and percentages of participants with at least one concomitant medication will be summarized by vaccination group and listed by Anatomical Therapeutic Chemical (ATC) level and preferred term. Preferred terms will be displayed in descending order of frequency of mRNA-1345.

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

6.2.5. Concomitant Procedures/Surgeries

Procedures and/or surgeries data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Imputation rules for missing/partial dates of procedures/surgeries are detailed in Appendix E.

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

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

Fraction of inspired oxygen (FiO_2) data will be listed.

6.2.6. Significant Protocol Deviations

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

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

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

6.2.7. COVID-19 Impact

An individual data listing on Coronavirus Disease 2019 (COVID-19) impact will be provided for the Randomization Set and it will include which visit(s)/assessment(s) has (have) been missed due to COVID-19, along with the specific relationship to COVID-19.

6.3. Efficacy Analysis

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.

6.3.1. Analysis of the Primary Efficacy Endpoints

The primary endpoints will be analyzed on the PPE Set in order to estimate Estimand 1a (refer to Appendix H). In addition, this will be supported by estimation of a treatment policy estimand (Estimand 1b) on the mITT set.

6.3.1.1. Primary Efficacy Endpoints Primary Definition/Derivation

The 2 primary efficacy endpoints are:

- VE of mRNA-1345 in preventing 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.
- VE of mRNA-1345 in preventing 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.

For each of the 2 primary efficacy endpoints, a RSV-LRTD case will be defined as a positive post-injection RT-PCR, together with eligible symptoms summarized in Table 3.

In the primary definition framework, RT-PCR results from the study's RT-PCR specialty laboratory will be used in the primary analysis. If specialty laboratory RT-PCR is not available, results with a regulatory approved (FDA or other agency) RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) will be used. If a participant has two nasopharyngeal (NP)-swabs collected on the same day, one tested at the specialty laboratory and another one tested at the certified laboratory, testing result from the specialty laboratory will be used. If multiple NP-swabs are collected on different days and tested at either laboratory, positive results will be used to confirm the RSV infection.

Table 3: RSV-LRTD

RSV-LRTD with 2 or more symptoms	
NP swab for RSV infection by RT-PCR	**Positive** result [1] **AND**
Symptoms	New or worsening of at least **TWO** 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 **OR** Radiologic evidence of pneumonia
RSV-LRTD with 3 or more symptoms	
NP swab for RSV infection by RT-PCR	**Positive** result [1] **AND**
Symptoms	New or worsening of at least **THREE** 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 **OR** Radiologic evidence of pneumonia

[1] RT-PCR results from the study's RT-PCR specialty laboratory will be used in the primary analysis. If specialty laboratory RT-PCR is not available, results with a regulatory approved (FDA or other agency) RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) will be used. If a participant has two NP-swabs collected on the same day, one tested at the specialty laboratory and another one tested at the certified laboratory, testing result from the specialty laboratory will be used. If multiple NP-swabs are collected on different days and tested at either laboratory, positive results will be used to confirm the RSV infection.

Eligible symptoms onset within 14 days of positive RSV RT-PCR specimen collection date (referring to "positive RSV RT-PCR date") will be included to derive a RSV-LRTD case. The date of the RSV-LRTD case will be the earlier date of the following two dates,

- Positive RSV RT-PCR date (as per derivations above)
- Date of eligible symptom(s), defined as earliest of

- Earliest date of the 1st eligible RSV-LRTD-like symptom reported
- Radiologic evidence date of pneumonia

Specifically, the date of RSV-LRTD will be the earlier date of two dates (positive RSV RT-PCR date and the date of eligible symptoms); the onset date of each eligible symptom and radiologic evidence date of pneumonia should be within 14 days of the positive RSV RT-PCR date.

Cases will be counted for each primary efficacy endpoint when the first occurrence of RSV-LRTD starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ≤ date of RSV-LRTD – date of injection ≤ 365. The time to the first occurrence of RSV-LRTD, in days, will be calculated as: date of confirmed RSV-LRTD – date of randomization + 1.

Duration of an RSV-LRTD case will be defined as the latest resolution date of the associated LRTD symptoms - the date of the RSV-LRTD case +1.

6.3.1.2. Primary Efficacy Endpoints Alternative Definition/Derivation

For sensitivity analysis, an alternative definition of both primary efficacy endpoints will be used.

The definition is similar to what specified in Section 6.3.1.1, but RT-PCR results from local laboratory tests will also be used, i.e. RT-PCR results from both specialty laboratory and non-certified laboratory, regardless of approved RT-PCR test kits.

For a given day, if RT-PCR results from the study's RT-PCR specialty laboratory are available, they will be used in the primary analysis. If specialty laboratory RT-PCR result is not available, results with a regulatory approved (FDA or other agency) RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) will be used. If no specialty laboratory RT-PCR results and no certified laboratory approved RT-PCR test kit results are available, results from a not certified or not approved RT-PCR test kits will be used. If a participant has two NP-swabs collected on the same day, one tested at the specialty laboratory and another one tested at the certified laboratory, testing result from the specialty laboratory will be used. If there is no result from a certified laboratory, the result form the non-certified laboratory or not approved RT-PCR test kits will be used. If multiple NP-swabs are collected on different days and tested at either laboratory, positive results will be used to confirm the RSV infection.

6.3.1.3. Primary Analysis Approach

Confidential

The primary analysis on each primary efficacy endpoint, following the primary definition, will be performed on the PPE Set.

The number and percentage of participants who had a case for the primary efficacy endpoint and participants who were censored will be summarized by vaccination group.

Vaccine efficacy (VE) is defined as the percent reduction in the hazard of the primary endpoint case (mRNA-1345 vs. placebo). VE will be estimated by one minus the hazard ratio (HR) (mRNA-1345 versus placebo), multiplied by 100:

$$VE = 100 \times [1 - HR] \%,$$

A stratified Cox proportional hazard model with study vaccination group as a fixed effect, adjusting for stratification factors at randomization, i.e., age group (≥ 60 to < 75 years or ≥ 75 years) and risk factors for LRTD (present versus absent), 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 analysis, participants who experience an early RSV-ARD case with date of the first case up to 14 days post injection will be censored at the date of the first case. Participants without an RSV-LRTD case up to 12 months will be censored at the earliest date of 12 months post injection, date of early discontinuation, date of death unrelated to RSV-LRTD, and data cutoff date.

To test null hypothesis for the primary endpoints, i.e., H^1_0: VE ⩽ 20% for RSV-LRTD cases with 2 or more symptoms and H^2_0: VE ⩽ 20% for RSV-LRTD cases with 3 or more symptoms, a 2-sided (1-2 × adjusted alpha) × 100% confidence intervals (CIs) for VE will be calculated based on the stratified Cox model and the corresponding 1-sided *p* value will be provided at the 2 planned IAs and primary analysis.

- Primary endpoint of VE for RSV-LRTD cases with 2 or more symptoms: The 1-sided adjusted alpha at IA1, IA2 and primary analysis will be 1.55%, 1.18% and 0.91% respectively, if the analyses are conducted at exactly 43, 74 and 86 cases, with overall 1-sided alpha for the primary endpoint = 2.5%.
- Primary endpoint of VE for RSV-LRTD cases with 3 or more symptoms: The 1-sided adjusted alpha at IA1, IA2 and primary analysis will be 1.55%, 1.18% and 0.91%

respectively, if the analyses are conducted at exactly 16, 28 and 32 cases, with overall 1-sided alpha for the primary endpoint = 2.5%.

The study will be considered to meet the primary efficacy objective if the lower bound of the 2-sided (1-2 × adjusted alpha) × 100% CI of VE rules out 20% either at IA1 or IA2 or primary analysis.

The above analysis corresponds to the Primary Efficacy Estimand 1a as described in Appendix H.

Cumulative incidence rates will be estimated based on the Kaplan-Meier method and plotted over time by vaccination group.

The descriptive statistics of the duration of the RSV-LRTD cases will also be provided.

6.3.1.4. Sensitivity Analysis

The following sensitivity analyses will be performed for each primary efficacy endpoint.

Sensitivity analysis 1: Analyses of primary endpoints will be conducted using the actual stratification factors derived from eCRF in the stratified Cox model based on the PPE Set using the same method and same definition as described in Section 6.3.1.3.

Sensitivity analysis 2: Analyses of the primary endpoints will be performed based on the mITT Set using the same method and same definition as described in Section 6.3.1.3. This sensitivity analysis corresponds to the Supportive Efficacy Estimand 1b as described in Appendix H.

Sensitivity analysis 3: Analyses of the primary endpoints with the same analysis method described in Section 6.3.1.3 will also be performed based on the PPE Set following the alternative definition as defined in Section 6.3.1.2, i.e. RT-PCR results from specialty laboratory, results with an approved RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) or results with a test kit from a non-certified laboratory.

Sensitivity analysis 4: Analyses of the primary endpoints with the same analysis method described in Section 6.3.1.3 will also be performed based on the PPE Set excluding the co-infection of any other non-RSV pathogens. The co-infection is defined as positive RT-PCR test result of any other non-RSV pathogen from a specialty laboratory based on a specimen that was collected on the same day as the positive RSV RT-PCR test result.

6.3.1.5. Supportive Analysis

The following supportive analyses will be performed for each primary efficacy endpoint.

Supportive analysis 1: Incidence rate will be provided for each vaccination group in the PPE set. Incidence rate will be calculated as the number of participants with an event (i.e. the first occurrence of RSV-LRTD at least 14 days after the injection up to 12 months after the injection) divided by the number of participants at risk adjusted by person-time (years) in each vaccination group. The person-time is calculated as the time from randomization to the date of the first event for participants with an event, and the time from randomization to the date of censoring for participants without an event (or who are censored, see detail in Section 6.3.1.1). Person-time, incidence rate, and 95% CI for incidence rate will be provided by vaccination group. VE will also be estimated by one minus the ratio of incidence rates (mRNA-1345 vs. placebo) multiplied by 100, i.e. 100% × (1- ratio of incidence rates (mRNA-1345 vs. placebo) 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.

Supportive analysis 2: Farrington and Manning's score method (Farrington and Manning 1990) will be performed for the primary efficacy endpoints to estimate VE with a 2-sided 95% CI in the PPE Set. VE is defined as the percent reduction in the risk of infection in the mRNA-1345 group, compared to the placebo group. VE will be estimated by one minus the ratio of cumulative incidences (mRNA-1345 versus placebo), multiplied by 100:

$$VE = 100 \times (1 - [(C_{mRNA} / N_{mRNA}) / (C_{control} / N_{control})]) \%,$$

where C_{mRNA} and $C_{control}$ are the number of RSV-LRTD cases per the primary definition in the mRNA-1345 group and the placebo group respectively, and N_{mRNA} and $N_{control}$ are the number of participants in the mRNA-1345 group and the placebo group, respectively.

These supportive analyses correspond to the Supportive Estimands 1c and 1d as described in Appendix H.

6.3.1.6. Subgroup Analysis

To assess consistency of VE across subgroups, subgroup analysis of each primary efficacy endpoint may be performed in selected subgroups based on the PPE Set, as appropriate. The primary efficacy endpoint will be analyzed by subgroup using the same methods described for the primary analysis (refer to Primary Efficacy Estimand 1a); the estimated VE and 95% CI will be provided within each category of the following subgroups:

- Risk factors for LRTD: CHF/COPD absent vs. present
- Age groups: ≥ 60 and < 75 years vs. ≥ 75 years
- Age groups: ≥ 60 and < 70 years, ≥ 70 and < 80 years, or ≥ 80 years
- Comorbidities of interest: 0 and ⩾ 1 pre-existing comorbidities of interest
- Frailty status: Fit (0 - 3), Vulnerable (4 - 5) or Frail (6 or more) based on Edmonton Frail Scale total score
- Sex: female vs. male
- Race: White, Black, Asian, or other (including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races)
- World bank region (North America/Europe, Central/Latin America/Africa, or Asian Pacific); details can be found in Appendix F.
- World bank country classifications by income level 2022 (Lower-middle-income economies, Upper-middle-income economies or High-income countries); details can be found in Appendix F.
- Ethnicity: Hispanic or Latino vs. Not Hispanic or Latino
- History of COVID-19: yes vs. no
- Hospitalization due to COVID-19: yes vs. no

If the number of participants in a subgroup is too small, it may be combined with other subgroups for the subgroup analyses. Forest plots may be provided for VE and its 95% CI of selected subgroup analyses based on the PPE Set. Subgroup analyses based on the mITT Set may be performed as needed.

6.3.2. Analysis of the Secondary Efficacy Endpoints

A hierarchical statistical multiple testing procedure (MTP) will be used to control the overall type I error rate 2.5% (1-sided) over the primary efficacy endpoints, key secondary efficacy endpoints, and other selected secondary efficacy endpoints. Key secondary efficacy endpoints and selected secondary efficacy endpoints will only be tested at the planned analysis at 12-month or final analysis, whichever is applicable, when both primary efficacy endpoints achieve statistical significance. See Section 6.5 for the multiplicity adjustments among the key secondary and other secondary efficacy endpoints.

RT-PCR results utilized in the derivation of all associated secondary efficacy endpoints, including the key secondary endpoints, will follow the same rule as specified in the primary definition of the primary efficacy endpoints (see Section 6.3.1.1). First, RT-PCR specialty laboratory will be used. If specialty laboratory RT-PCR is not available, results with a regulatory approved (FDA or other agency) RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) will be used. If a participant has two NP-swabs collected on the same day, one tested at the specialty laboratory and another one tested at the certified laboratory, testing result from the specialty laboratory will be used. If multiple NP-swabs are collected on different days and tested at either laboratory, positive results will be used to confirm the RSV infection.

6.3.2.1. Derivation of Cases for Key Secondary Efficacy Endpoints

RSV-ARD within the period of 14 days post-injection up to 12 months post-injection

The first key secondary efficacy endpoint is the VE of mRNA-1345 in preventing the first occurrence of protocol-defined RSV-ARD within the period of 14 days post-injection up to 12 months post-injection. An RSV-ARD case will be defined as a positive post-injection RT-PCR result, together with eligible symptoms, as summarized in Table 4:

Table 4: RSV-ARD

	RSV-ARD
NP swab for RSV infection by RT-PCR	**Positive** result [1] **AND**

Symptoms	New or worsening of at least **ONE** of the following: 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 **OR** Radiologic evidence of pneumonia

[1] RT-PCR results from the study's RT-PCR specialty laboratory will be used in the primary analysis. If specialty laboratory RT-PCR is not available, results with a regulatory approved (FDA or other agency) RT-PCR test kit from a certified laboratory (CLIA or CLIA equivalent) will be used. If a participant has two NP-swabs collected on the same day, one tested at the specialty laboratory and another one tested at the certified laboratory, testing result from the specialty laboratory will be used. If multiple NP-swabs are collected on different days and tested at either laboratory, positive results will be used to confirm the RSV infection.

Eligible symptoms onset within 14 days of positive RSV RT-PCR specimen collection date (referring to RSV RT-PCR date) will be included to derive a RSV-ARD case. The date of the RSV-ARD case will be the earlier date of the following two dates:

- Positive RSV RT-PCR date (see detailed definition in Table 4),
- Date of eligible symptoms, defined as earliest of:
    - Earliest date of the 1st eligible RSV-ARD-like symptoms reported.
    - Radiologic evidence date of pneumonia.

The date of RSV-ARD will be the earlier date of two dates (positive RSV RT-PCR date, and the date of eligible symptoms); the onset date of each eligible symptom and radiologic evidence date of pneumonia should be within 14 days of the positive RSV RT-PCR date.

Cases will be counted for the key secondary efficacy endpoint when the first occurrence of RSV-ARD starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ≤ date of RSV-ARD – Date of injection ≤ 365.The time to the first occurrence of RSV-ARD, in days, will be calculated as: date of confirmed RSV- ARD – date of randomization + 1.

Duration of an RSV-ARD case will be defined as the latest of the associated symptoms resolution date - the date of the RSV-ARD case +1.

Hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection

The second key secondary efficacy endpoint is the VE of mRNA-1345 in preventing the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection.

A case of hospitalization associated with RSV-ARD or RSV-LRTD will be defined as a hospitalization that is associated with an RSV-LRTD (case for the first primary efficacy endpoint) or an RSV-ARD (case for the first key secondary efficacy endpoint). A case is defined if: (1) The investigator assesses, in the Adverse Events eCRF page, that an event is a confirmed diagnosis of RSV-LRTD or RSV-ARD and that requires inpatient or prolongation of existing hospitalization; (2) either a primary efficacy case of RSV-LRTD or a key secondary efficacy case of RSV-ARD is defined based on Sections 6.3.1.1 and 6.3.2.1; (3) derived RSV-LRTD or RSV ARD-Case date is within 14 days prior to or during hospitalization, i.e. hospitalization admission date -14 days ≤ derived RSV-LRTD/RSV-ARD case date ≤ hospitalization discharge date. The date of the first hospitalization associated with RSV-ARD or RSV-LRTD will be the earliest date of RSV-ARD and RSV-LRTD dates (as derived based on Sections 6.3.1.1 and 6.3.2.1). Cases will be counted for the key secondary efficacy endpoint when the date of the first eligible hospitalization associated with RSV-LRTD or RSV-ARD starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ≤ date of RSV-LRTD/RSV-ARD – Date of injection ≤ 365.

The time to the first hospitalization associated with RSV-ARD or RSV-LRTD, in days, will be calculated as: date of RSV-LRTD/RSV-ARD – Date of randomization + 1

6.3.2.2. Analysis of the Key Secondary Efficacy Endpoints

The similar primary, sensitivity, and supportive analysis methods as for the primary efficacy endpoints (Sections 6.3.1.3, 6.3.1.4, 6.3.1.6) will be applied for the following key secondary endpoints based on the PPE Set, unless otherwise specified:

- VE to prevent the first occurrence of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection

- VE to prevent the first hospitalization associated with RSV-ARD or RSV--LRTD within the period of 14 days post-injection up to 12 months post-injection

For each of the above endpoints, the following analyses will be conducted at the planned primary analysis or final analysis:

- Primary analysis: VE will be estimated with 100% × [1 - HR ratio] with 2-sided 95% CI, using the stratified Cox model based on the PPE Set.
- Sensitivity analysis 1: The same analysis as the primary analysis using the actual stratification factors derived from eCRF.
- Sensitivity analysis 2: The same analysis as the primary analysis based on the mITT Set.
- Sensitivity analysis 3: The same analysis as the primary analysis based on the PPE Set by using RT-PCR results from both specialty laboratory and non-certified laboratory regardless of approved RT-PCR test kits.
- Sensitivity analysis 4: The same analysis as the primary analysis based on the PPE Set by excluding co-infection of any other non-RSV pathogen.
- Supportive analysis 1: Exact method based on incidence rate and the PPE Set.
- Supportive analysis 2: Farrington and Manning's score method based on the PPE Set.
- Subgroup analysis: The same analysis as the primary analysis by the same subgroups specified for subgroup analysis of the primary efficacy endpoints.

For the key secondary endpoint regarding RSV-ARD, the descriptive statistics of the duration of the RSV-ARD case will also be provided.

6.3.2.3. Derivation of Cases and Endpoints for Other Secondary Efficacy Endpoints

All-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection

With respect to the VE of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection, an all-cause hospitalization case will be

defined as any reported hospitalization which is collected as inpatient or prolongation of existing hospitalization in the eCRF AE form.

The date of an all-cause hospitalization case will be the admission date of the hospitalization. Cases will be counted when the all-cause hospitalization date starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ≤ date of hospitalization – date of injection ≤ 365.

All-cause LRTD within the period of 14 days post-injection up to 12 months post-injection

Respiratory Illness Episodes:

When a participant is determined to have one potential respiratory illness episode of all-cause LRTD, the participant will be arranged to have an unscheduled illness visit with eligible symptoms entered in RSV Symptoms Log eCRF page.

Symptoms within one respiratory illness episode are collected under the same folder name in eCRF. For two adjacent illness episodes, when there is no missing resolution date for any eligible symptom, if the earliest eligible symptom of the second illness episode starts at least 7 days after the latest symptom resolution date of the first episode, these two illness episodes will be considered as two separate episodes. Otherwise, these two adjacent illness episodes will be considered as one episode. When a resolution date of any eligible symptoms in the first illness episode is missing (e.g., resolution dates of ongoing symptoms are captured as missing), and the interval between the earliest eligible symptom onset dates of two adjacent episodes is at least 28 days, these two illness episodes will be considered as two separate episodes. Otherwise, these two illness episodes will be considered as one episode.

Derivation of all-cause LRTD:

With respect to the VE of mRNA-1345 to prevent all-cause LRTD within the period of 14 days post-injection up to 12 months post-injection, an all-cause LRTD case will be defined by eligible symptoms, as summarized in Table 5:

Table 5: All-cause LRTD

	All-cause LRTD
Symptoms	New or worsening of at least **TWO** of the following symptoms within a respiratory illness episode:

	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 **OR** Radiologic evidence of pneumonia

The detailed derivation logic of all-cause LRTD cases is listed below:

- If there is no radiologic evidence of pneumonia within a respiratory illness episode having at least 2 LRTD symptoms, the date of the all-cause LRTD case will be the earliest date of the 1st eligible LRTD symptom reported within the illness episode.
- If there is a radiologic evidence of pneumonia within a respiratory illness episode (i.e., the date of radiologic evidence of pneumonia is no earlier than the earliest onset date of the symptoms within a respiratory illness episode and no later than the latest resolution date of the symptoms within a respiratory episode), the date of the all-cause LRTD case will be the earlier date of 1) the earliest date of the 1st eligible LRTD symptom reported within the illness episode and 2) date of radiologic evidence of pneumonia.
- If the date of radiologic evidence of pneumonia is not within a respiratory illness episode as stated above, and at least 28 days after the earliest onset date of the 1st symptom of a previous respiratory episode, the radiologic evidence of pneumonia will be considered as a separate all-cause LRTD case that is not part of the previous respiratory episode; otherwise, the radiologic evidence of pneumonia will be considered as part of the previous respiratory episode, and the date of the all-cause LRTD will be the earlier date of 1) the earliest date of the 1st eligible LRTD symptom reported within the illness episode and 2) date of radiologic evidence of pneumonia.

Cases will be counted when the occurrence of all-cause LRTD starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ≤ date of all-cause LRTD – Date of injection ≤ 365.

RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection

With respect to the VE of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more (or 3 or more) symptoms within the period of 14 days post-injection up to 24 months post-injection, derivation of the case will be similar to that for the primary efficacy endpoints in Section 6.3.1.1; cases will be counted when the first occurrence of RSV-LRTD starts 14 days after the injection and up to 730 days after the injection, i.e. 14 ≤ date of RSV-LRTD –date of injection ≤ 730.

RSV-LRTD by RSV subtype A and subtype B, respectively

The derivation of the first RSV-LRTD case with 2 or more (or 3 or more) symptoms by subtype A and subtype B will be similar to that for the primary efficacy endpoints in Section 6.3.1.1; cases by subtype A and subtype B, respectively, will be derived for both periods of 14 days post-injection up to 12 months post-injection, and 14 days post-injection up to 24 months post-injection.

Hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection

The derivation of the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection will be similar to that for the second key secondary efficacy endpoint in Section 6.3.2.1. Cases will be counted when the date of the first eligible hospitalization associated with RSV-LRTD or RSV-ARD starts 14 days after the injection and up to 730 days after the injection, i.e. 14 ⩽ date of RSV-LRTD/RSV-ARD – date of injection ≤ 730; participants without a case identified up to 24 months will be censored at the earliest date of 24 months (Day 730), date of early discontinuation, date of death unrelated to RSV-ARD or RSV-LRTD, and data cutoff date. Participants who experience an early RSV-ARD from Day 1 to Day 14 will be censored at the date of the RSV-LRTD/RSV-ARD in the PPE analysis.

Change in Total Frailty Score from Baseline to 12 months and 24 months post-injection

The Edmonton Frail Scale (EFS) is used for total frailty score, the derivation of total frailty score from baseline to 12 months and 24 months post-injection is described in Section 6.3.2.4.

6.3.2.4. Analysis of Secondary Efficacy Endpoints

A negative binomial regression model will be applied for the following secondary efficacy endpoints based on the PPE Set, unless otherwise specified:

- VE to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection
- VE to prevent all-cause LRTD within the period of 14 days post-injection up to 12 months post-injection.

VE will be estimated by one minus the ratio of model estimated event rates (mRNA-1345 vs. placebo) multiplied by 100. Ratio of model estimated event rates is based on a negative binomial regression model with vaccination group and stratifications factors at randomization as covariates and the logarithm of person-time as an offset variable. The person-time is calculated as the time from randomization date to 12 months, date of early discontinuation, date of unrelated death, or data cutoff date, whichever is the earliest. The VE, ratio of model estimated event rates and 95% CIs will be presented.

Additionally, the number and percentage of participants by count of events (i.e. all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection), total number of events, total person-time in years, raw event rate, model estimated event rate and 95% CI for model estimated event rate will be also provided for each vaccination group.

The similar primary analysis method as for the primary efficacy endpoints (Section 6.3.1.3) will be applied for the following secondary efficacy endpoints based on the PPE Set, unless otherwise specified:

- VE to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 24 months post-injection
- VE to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 24 months post-injection
- VE to prevent the first episode of RSV-LRTD with 2 or more within the period of 14 days post-injection up to 12 months post-injection symptoms by RSV subtype A and RSV subtype B

- VE to prevent the first episode of RSV-LRTD with 3 or more within the period of 14 days post-injection up to 12 months post-injection symptoms by RSV subtype A and RSV subtype B
- VE to prevent the first episode of RSV-LRTD with 2 or more within the period of 14 days post-injection up to 24 months post-injection symptoms by RSV subtype A and RSV subtype B
- VE to prevent the first episode of RSV-LRTD with 3 or more within the period of 14 days post-injection up to 24 months post-injection symptoms by RSV subtype A and RSV subtype B
- VE to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection

VE will be estimated with 100% × [1 - HR] with 2-sided 95% CI based on the PPE Set, using the stratified Cox model with study vaccination group as a fixed effect, adjusting for stratification factors at randomization.

Cases occurred within the period of 14 days post-injection up to 12 months post-injection will use the same censoring rule as described in Section 6.3.1.3. Participants who experience an early RSV-ARD case with date of the first case up to 14 days post-injection will be censored at the date of first case, participants without an RSV-LRTD case up to 24 months will be censored at the earliest date of 24 months (Day 730), date of early discontinuation, date of death unrelated to RSV-LRTD, and data cutoff date.

In addition, the same analysis based on PPE set will be performed for VE to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 12 months post-injection up to 24 months post-injection. The analysis for other VE endpoints within the period of 12 months post-injection up to 24 months post-injection may be performed, using the exact method as specified in Section 6.3.1.5.

The total frailty score is the sum of individual scores from the 9 domains included in the Edmonton Frail Scale which is a multidimensional frailty assessment scale that assess domains related to frailty, including cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. The total frailty score ranges between 0 and 17. An analysis of covariance model based on the PPE Set with change in Confidential

total frailty score from baseline to 12 months post-injection as dependent variable, the vaccination group as explanatory variable, adjusting for the stratification factors at randomization, with baseline total frailty score as a covariate, will be used to assess the vaccination effect for the change in total frailty score from baseline to 12 months. A similar analysis of covariance model based on the PPE Set will be used to assess the vaccination effect for the change in total frailty score from baseline to 24 months

6.3.3. Analysis of Exploratory Efficacy Endpoints

Exploratory analyses of efficacy described in this section will not be performed at the interim analyses and may be performed at the primary analysis, 12-month analysis or final analysis, as appropriate.

For the following exploratory endpoints, estimate of VEs and the corresponding 95% CIs based on a negative binomial regression model will be provided using the PPE Set.

- VE of mRNA-1345 to prevent or mitigate all-cause LRTD with at least 3 or 4 symptoms or signs of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection. A separate analysis will be conducted based on each threshold.
- VE of mRNA-1345 to prevent or mitigate all-cause LRTD with at least 3 or 4 symptoms or signs of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection. A separate analysis will be conducted based on each threshold.
- VE of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent all-cause ARD within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent all-cause LRTD within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent all-cause ARD within the period of 14 days post-injection up to 24 months post-injection.

For the following exploratory endpoints, estimate of VEs and the corresponding 95% CIs based on the stratified Cox model will be provided using the PPE Set:

- VE of mRNA-1345 to prevent or mitigate the first RSV-LRTD with at least 4 symptoms or signs of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent or mitigate the first RSV-LRTD with at least 4 symptoms or signs of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection. VE of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent RSV-LRTD with shortness of breath and at least 1 other symptom or sign of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent RSV-LRTD with hypoxemia and tachypnea as two signs of lower respiratory tract involvement within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent RSV-LRTD with shortness of breath and at least 1 or 2 other symptoms or signs of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent RSV-LRTD with hypoxemia and tachypnea as two signs of lower respiratory tract involvement within the period of 14 days post-injection up to 24 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.

- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
- VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 24 months post-injection.

The number and percentage of participants with the first episode of 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 and within the period of 14 days post-injection up to 24 months post-injection will be provided by vaccination group and baseline frailty status (EFS; 0-3: Fit, 4-5: Vulnerable, 6-7: Mild Frailty, 8-9: Moderate Frailty, 10 or more: Severe Frailty). Similar summaries will be provided for the number of participants with RSV-ARD.

For the endpoint of VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case within the period of 14 days post-injection up to 12 months post-injection, it is defined as the first hospitalization due to respiratory SAE that occurred within 28 days from the RSV RT-PCR positive test result date (either from specialty or local lab), i.e., -28 $\leqslant$ Date of hospitalization admission - Date of RT-PCR positive test result date $\leqslant$ 28. Respiratory SAE is based on pre-specified MedDRA coding selected by clinicians with expertise in respiratory infections. The date of a case for this exploratory endpoint will be the hospitalization admission date. Cases will be counted when the date of case starts 14 days after the injection and up to 365 days after the injection, i.e. 14 $\leqslant$ Date of hospitalization admission– Date of injection $\leq$ 365. The time to the first hospitalization associated with an RSV positive case, in days, will be calculated as: Date of hospitalization admission – Date of randomization + 1.

For the endpoint of VE of mRNA-1345 to prevent the first hospitalization associated with an RSV positive case and/or use of supplemental oxygen as compared with placebo within the period of 14 days post-injection up to 12 months post-injection, a case will be defined as: (1) a hospitalization that is associated with an RSV positive case (case for the exploratory efficacy endpoint defined in the previous paragraph), and/or (2) a supplemental oxygen use collected on Confidential

Supplemental Oxygen eCRF starting within 28 days from the RSV RT-PCR positive test result date (either from specialty or local lab), i.e., -28 ⩽ Start date of oxygen use - Date of RT-PCR positive test result date ⩽ 28. The date of a case for this exploratory endpoint will be the earliest date of the hospitalization admission date and the oxygen use start date. Cases will be counted when the date of case starts 14 days after the injection and up to 365 days after the injection, i.e. 14 ⩽ Date of case– Date of injection ≤ 365. The time to the first hospitalization associated with an RSV positive case or use of supplemental oxygen, in days, will be calculated as: Date of case– Date of randomization + 1.

Analyses will be performed, as needed, on the second episode of RSV-LRTD with 2 or more (or 3 or more) symptoms. The second episode of RSV-LRTD with 2 or more (or 3 or more) symptoms is a recurrent RSV-LRTD with symptoms starting 14 days after symptom resolution of the first episode. The number and percentage of participants with the second episode of RSV-LRTD with 2 or more (or 3 or more) symptoms will be provided by vaccination group.

The time to the second episode of RSV-LRTD with 2 or more (or 3 or more) symptoms from the first episode of RSV-LRTD with 2 or more (or 3 or more) symptoms, in days, will be calculated only for those participants with the first episode of RSV-LRTD as: Date of the second episode of RSV-LRTD – Resolution date of the first episode of RSV-LRTD + 1. Kaplan-Meier curves will be used to plot the estimated cumulative incidence rates over time by vaccination group. Censoring rules, as reported in Section 6.3.1.1, will be used.

The number of RSV-LRTD with 2 or more (or 3 or more) symptoms episodes through 12 months post-injection will be summarized descriptively by vaccination group. The derivation of RSV-LRTD with 2 or more (or 3 or more) symptoms is specified, in Section 6.3.1.1. An episode is considered recurrent when eligible symptoms onset 14 days after symptom resolution of the previous episode.

The number of participants with the first episode of RSV-LRTD with 2 or more (or 3 or more) symptoms and the number of participants with the first episode of RSV-ARD up to 12 months and 24 months post-injection will be summarized 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.

Additionally, the number and percentage of deaths from all causes at 12 months and 24 months post-injection will be provided by vaccination group.

The following exploratory endpoints and associated analyses will be included in a separate analysis plan and performed by a separate health economics and outcomes research (HEOR) vendor.

- Number of participants in each baseline and subsequent worst living situation.
- VE of mRNA-1345 to prevent exacerbations of CHF up to 12 months and 24 months post-injection.
- VE of mRNA-1345 to prevent exacerbations of COPD up to 12 months and 24 months post-injection.
- Change from baseline in health-related quality of life (HRQoL) using the 5 level EuroQol 5 Dimension (EQ-5D-5L) utility index scores at 12 months and 24 months.
- Change from baseline in HRQoL for participants with RSV-LRTD or RSV-ARD using the EQ-5D-5L utility index scores at 12 months and 24 months
- 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 at the start of the symptoms (baseline), and at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms.
- Healthcare-related endpoints:
    - Number of participants with 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
- Number of participants with new prescriptions for medications including antibiotics associated with RSV-LRTD or RSV-ARD and with all-cause LRTD or all-cause ARD

6.4. Planned Analyses

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 vaccination 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 $\leqslant$ 0.2 (equivalently, HR $\geqslant$ 0.8) and H^2_0: VE $\leqslant$ 0.2 (equivalently, HR $\geqslant$ 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 as long as 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 as long as 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 as long as 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.

If the success criterion of the primary objectives of VE is successfully met at either the first IA or the second IA, selected Sponsor and CRO personnel, as defined in the Data Blinding Plan (DBP), will be unblinded per the DSMB review and recommendation to prepare the package for regulatory submissions.

In the situation that the success criterion of neither IA is met, the study would be considered as still successfully meeting the success criteria of the primary objectives of VE at the primary analysis if the lower bound of the 2-sided 98.18% CI of VE rules out 20% in the PPE Set. Selected Sponsor and CRO personnel, as defined in the DBP, will be unblinded for the Primary Analysis result.

If the success criterion is met at either IA or the primary analysis, all participants will continue their subsequent study follow-up until reaching the Month 24 Visit.

An independent, unblinded CRO statistical team will carry out IAs, the primary analysis and the potential 12-month analysis, as outlined in the DBP. The unblinded CRO statistical team would not be involved in either study design or the regular study conduct. Except for appropriately delegated unblinded pharmacists, vaccine administrators, clinical trial managers, and monitors, and selected Sponsor and CRO personnel to be unblinded per the DBP, all other personnel involved in the conduct of the study will remain blinded until the final analysis, which will be performed after all participants have completed the month 24 follow-up and after the database is cleaned and locked.

6.5. Multiplicity Adjustment

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 2 primary, 2 key secondary and 3 selected secondary endpoints (Figure 2).

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 pre-defined order as shown in Figure 2 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.

A sequential testing of key secondary endpoints will be performed at a 1-sided type I error rate of 2.5%.

- First, hypothesis testing against the null hypothesis, H^3_0: VE to prevent the first RSV-ARD (within the period of 14 days post-injection up to 12 months post-injection) $\leqslant$ 20%, will be performed. If the lower bound of the 2-sided 95% CI of VE of RSV-ARD > 20%, H^3_0 can be rejected.
- Once H^3_0 is rejected, the subsequent null hypothesis, H^4_0: VE to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD (within the period of 14 days

post-injection up to 12 months post-injection) $\leqslant$ 20% will be tested. If the lower bound of the 2-sided 95% CI of VE of the first hospitalization associated with RSV-ARD or RSV-LRTD > 20%, H^4_0 can be rejected.

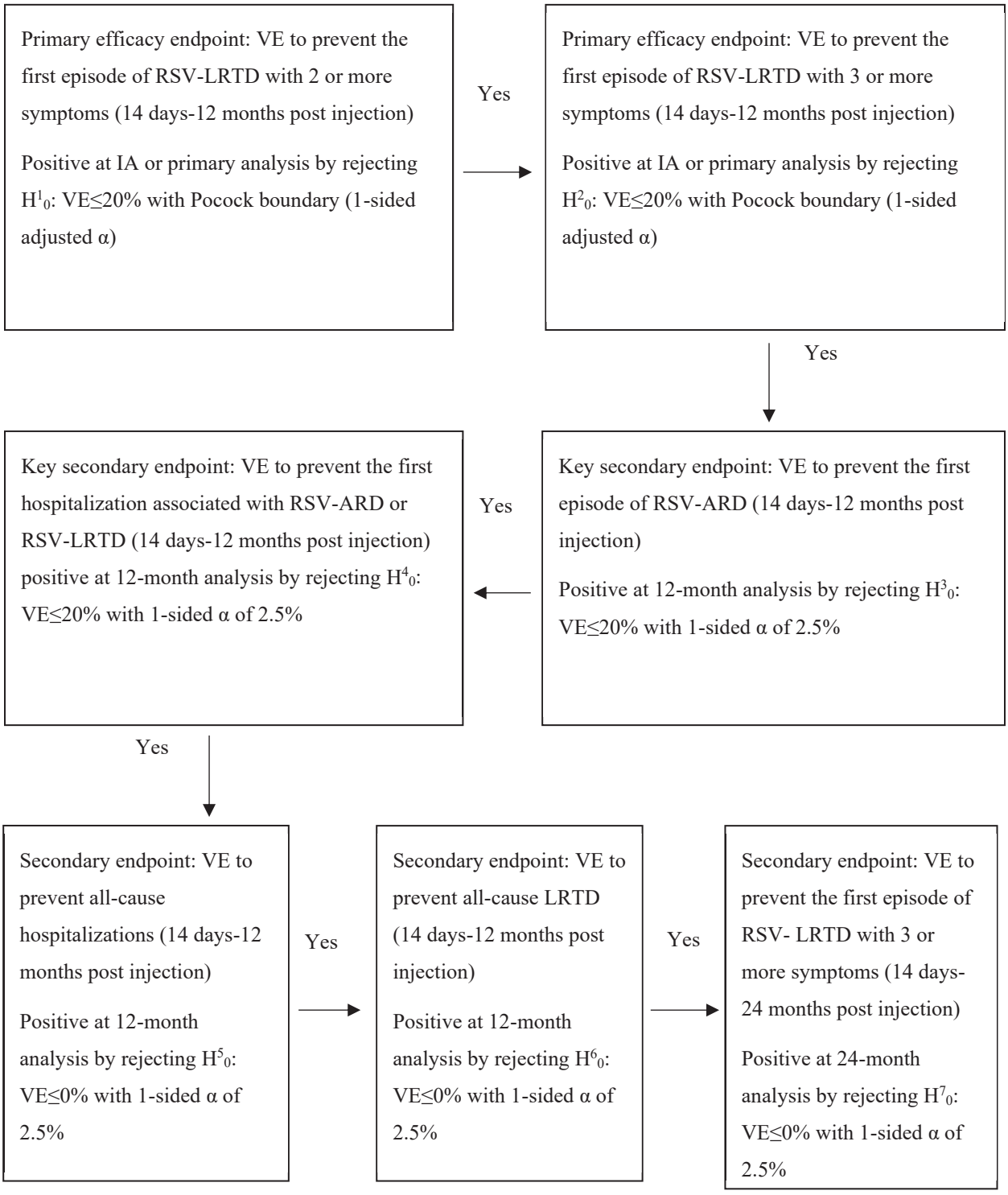
If the two key secondary efficacy endpoints achieve statistical significance without breaking above sequence, a sequential testing of three selected secondary efficacy endpoints will be performed at 12-month analysis/final analysis at a 1-sided Type I error rate of 2.5%:

- Once H^4_0 is rejected, the subsequent null hypothesis, H^5_0: VE to prevent all-cause hospitalizations (within the period of 14 days post-injection up to 12 months post-injection) $\leqslant$ 0% will be tested. If the lower bound of the 2-sided 95% CI of VE of all-cause hospitalizations > 0%, H^5_0 can be rejected.
- Once H^5_0 is rejected, the subsequent null hypothesis, H^6_0: VE to prevent all-cause LRTD (within the period of 14 days post-injection up to 12 months post-injection) $\leqslant$ 0%, will be tested. If the lower bound of the 2-sided 95% CI of VE of all-cause LRTD > 0%, H^6_0 can be rejected.
- Once H^6_0 is rejected, the subsequent null hypothesis, H^7_0: VE to prevent RSV-LRTD with 3 or more symptoms (within the period of 14 days post-injection up to 24 months post-injection) $\leqslant$ 0% will be tested. If the lower bound of the 2-sided 95% CI of VE of RSV-LRTD > 0%, H^7_0 can be rejected.

No further testing will be performed once the sequence breaks, that is, further testing stops as soon as an endpoint in the sequence fails to show statistical significance against the null hypothesis.

Analyses of remaining other secondary efficacy endpoints are not controlled for multiplicity.

Figure 2 Testing Sequence of Primary and Key and Secondary Efficacy Endpoints



6.6. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to study discontinuation, vital signs, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA version 25.0. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study for the collection and severity grading of solicited ARs as presented in Table 8 of the study protocol.

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.

6.6.1. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). An eDiary will solicit daily the participant on the occurrence and intensity of selected signs and symptoms using a pre-defined structured checklist.

Any solicited ARs reported during the 7-day follow-up post-injection, if not reported in the eDiary, should be reported in the Reactogenicity eCRF. Solicited ARs reported in both the eCRF and eDiary will be included in the evaluation of solicited ARs.

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 (aches in several joints), nausea/vomiting, chills and fever.

The solicited ARs will be graded based on the grading scales presented in Table 8 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days post-injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution, not to exceed 28 days after study injection.

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

Analyses of solicited ARs will be provided by vaccination group based on the Solicited Safety Set.

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

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

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

The above analyses of solicited ARs may be provided for the following subgroups, as applicable:

- Age group (60 to 69 years, 70 to 79 years, $\geq$ 80 years)

- Sex (male, female)
- Comorbidities of interest: 0 and ≥ 1 pre-existing comorbidities of interest
- Frailty status: Fit (0 - 3), Vulnerable/Frail (4 or more) based on Edmonton Frail Scale total score
- Race
- Ethnicity
- World bank region (North America/Europe, Central/Latin America/Africa, or Asian Pacific); details can be found in Appendix F

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

6.6.2. Unsolicited Treatment-emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not present before exposure to the IP or any event already present that worsens in intensity or frequency after exposure to IP. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner, where the participant seeks medical attention outside normal study procedures. AESIs for this study are pre-defined in the protocol Appendix I, Table 14 including thrombocytopenia, neurologic diseases, anaphylaxis, and myocarditis/pericarditis.

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

- TEAEs that are reported by participants and recorded on the AE eCRF
- Solicited ARs that meet SAE criteria or last beyond 7 days after injection and are recorded on the Reactogenicity eCRF

Unsolicited AEs will be collected for up to 28 days after IP injection; SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be collected throughout the study. Analyses of unsolicited TEAEs will be provided for up to 28 days after IP injection unless otherwise specified. Additionally, SAEs, MAAEs, AESIs and AEs leading to study discontinuation will be summarized throughout the study (up to Day 730/End of Study). Refer to Safety Estimands 2b, 2c, 2d, 2e and 2f in Appendix H.

All summary tables (except for the overall summary of TEAEs) for unsolicited TEAEs will be presented by SOC and PT or by PT only for TEAEs with counts of participants included. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1345 group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same TEAE or a continuing TEAE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

For the by-severity summaries, the toxicity grade of a solicited AR meeting SAE criteria or lasting beyond 7 days after injection will be mapped to a severity level of Mild/Grade 1, Moderate/Grade 2 or Severe/ $\geq$ Grade 3 and the maximum severity level in the case of multiple events will be presented.

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

In addition, the number of events and number of participants with occurrences of selected TEAEs of clinical interests identified by SMQ in up to 7 days after injection, up to 28 days after injection, and throughout the study will be summarized. SMQ will be summarized by subordinate SMQ, and PT, if applicable. Two sets of summary tables will be provided, one will be based on combined broad and narrow scope of SMQ, the other will be based on narrow scope. SMQ and subordinate SMQ within each SMQ will be displayed in alphabetic order. PTs will be displayed in descending order of frequency in the mRNA-1345 group and then alphabetically within subordinate SMQ or SMQ if no subordinate SMQ.

Detailed descriptions of selected SMQ are presented in Appendix J, Table 15 and Table 16.
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6.6.2.1. Overview of Unsolicited TEAEs

An overall summary of unsolicited TEAEs up to 28 days after injection will include the number and percentage of participants who experience at least one of the following categories:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs
- Any unsolicited TEAEs leading to study discontinuation
- Any unsolicited severe/>=Grade3 TEAEs
- Any unsolicited non-serious TEAEs
- Any unsolicited non-serious severe/>=Grade3 TEAEs
- Any unsolicited AESI

Note: Severe TEAEs include both unsolicited severe TEAEs and >= Grade 3 solicited ARs that meet SAE criteria or last beyond 7 days after injection.

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

The overall summary of all the above categories will be also provided for unsolicited TEAEs up to 7 days after injection, and between 8 and 28 days after injection. Additionally, the overall summary for the categories of SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be provided for these TEAEs throughout the study.

In addition, separate listings containing individual participant AE data for unsolicited TEAEs, treatment-related TEAEs, severe TEAEs, treatment-related severe TEAEs, TEAEs leading to study discontinuation, serious AEs, serious treatment-related AEs, medically-attended TEAEs, treatment-related medically-attended TEAEs, TEAEs leading to death, and TEAEs of AESIs will be provided. Listing of deaths including cause of death, and listing of TEAEs in participants who died will be provided.

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6.6.2.2. TEAEs by System Organ Class and Preferred Term

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

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited severe (severe/>=Grade 3) TEAEs
- All unsolicited severe (severe/>=Grade 3) TEAEs that are treatment-related
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related
- All unsolicited TEAEs leading to study discontinuation
- All unsolicited treatment-emergent AESIs
- All unsolicited non-serious TEAEs
- All unsolicited non-serious severe (severe/>=Grade 3) TEAEs
- All unsolicited TEAEs leading to death

Note: Severe TEAEs include both unsolicited severe TEAEs and >=Grade 3 solicited ARs that meet SAE criteria or last beyond 7 days after injection.

A summary of TEAEs with rate difference and the corresponding 95% CI using the Miettinen-Nurminen's method will be provided, for PTs reported by at least 0.1% of participants in any vaccination group.

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

Additionally, summary tables of serious AEs, MAAEs, treatment-related MAAEs, TEAEs leading to study discontinuation, AESIs, and TEAEs leading to death will be also be provided by SOC and PT considering all events reported throughout the study.

6.6.2.3. TEAEs by Preferred Term

The following summary tables of TEAEs will be provided by PT sorting by frequency on the mRNA-1345 group:

- All unsolicited TEAEs up to 28 days after injection
- All serious TEAEs up to 28 days after injection
- All serious TEAEs throughout the study
- SMQ up to 28 days after injection
- SMQ throughout the study

6.6.2.4. TEAEs by Severity

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

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

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

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

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

6.6.2.6. Independent Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in Protocol Section

8.4.3) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

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

6.6.2.7. Subgroup Analysis of TEAEs

The overview of TEAEs, TEAEs by SOC/PT will be provided for the following subgroups:

- Age group (60 to 69 years, 70 to 79 years, ≥ 80 years)
- Sex (male, female)
- Comorbidities of interest: 0 and ≥ 1 pre-existing comorbidities of interest
- Frailty status: Fit (0 - 3), Vulnerable/Frail (4 or more) based on Edmonton Frail Scale total score
- Race
- Ethnicity
- World bank region (North America/Europe, Central/Latin America/Africa, or Asian Pacific); details can be found in Appendix F

6.6.3. Vital Sign Measurements

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.

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

Observed values and changes from pre-injection to post-injection on Day 1 for all vital sign measurements will be summarized by vaccination group. Shift from pre-injection to post-injection in the toxicity grades will be summarized by vaccination group.

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

6.7. Immunogenicity Analysis

There are two objectives on immunogenicity in this study: to evaluate the antibody response to a single dose of mRNA-1345 vaccine from baseline to 24 months post-injection (secondary objective) and to assess correlates of risk and protection (exploratory objective).

This SAP includes analyses of immunogenicity data for the secondary immunogenicity objective. The analysis of assessing correlates of risk and protection will be included in a separate Immune Correlates SAP.

To characterize immunogenicity of mRNA-1345, immunogenicity data will be analyzed using the PPI set for Immunogenicity (Section 6.7.2).

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

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

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

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

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

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

6.7.1. Sampling of the Immunogenicity Subset (Case-Cohort Sampling Design)

Details of the case-cohort sampling design are provided in a separate Immunogenicity Sampling Plan.

6.7.2. Analysis Set for Immunogenicity Analysis

The PPI Set will be used as the analysis population to characterize immunogenicity of mRNA-1345, unless otherwise specified.

6.7.3. Immunogenicity Data

Immunogenicity assessments will include the following:

- Serum nAb level to RSV-A and RSV-B
- Serum bAb level to RSV (pre-fusion and/or post-fusion)
- 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 cell based microneutralization 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.

6.7.4. Summary of Antibody-Mediated Immunogenicity Endpoints

Immunogenicity data are collected at the pre-specified timepoints: baseline (Day 1), Day 15 (on Phase 2 only), Day 29, Day 181, Day 365, Day 546 and Day 730. The following summaries will be provided.

- GMT of RSV-A nAbs, RSV-B nAbs and GMC of RSV bAbs (pre-fusion and/or post-fusion) with corresponding 95% CI will be provided at each time point. 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. The following descriptive statistics will be also provided at each time point: the number of participants (n), median, minimum and

maximum. GMT or GMC with 95% CI will be plotted at baseline (Day 1) and Day 29 by vaccination group. Reverse cumulative distribution function plot may also be provided.

- SRR of RSV-A nAbs, RSV-B nAbs and RSV bAbs at each post-baseline time point will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.
- GMFR of RSV-A nAbs, RSV-B nAbs and RSV bAbs (pre-fusion and/or post-fusion) with corresponding 95% CI will be provided at each post-baseline timepoint over baseline at Day 1. 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. GMFR and corresponding 95% CI will be plotted at each timepoint.
- Proportion of participants with ≥ 2-fold increases from baseline in RSV-A nAb titers, RSV-B nAb titers, and RSV bAbs (pre-fusion and/or post-fusion) concentration at each post-baseline time point will be provided with 2-sided 95% CIs using the Clopper-Pearson method by vaccination group.

6.7.5. Subgroup Analysis

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

- Risk factors for LRTD: CHF/COPD absent vs. present
- Age groups: ≥ 60 and < 75 years vs. ≥ 75 years
- Age groups: ≥ 60 and < 70 years, ≥ 70 and < 80 years, or ≥ 80 years
- Comorbidities of interest: 0 and ⩾ 1 pre-existing comorbidities of interest
- Frailty subgroup
- Sex: female vs. male
- Race: White, Black, Asian, or other (including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races)
- World bank region (North America/Europe, Central/Latin America/Africa, or Asian Pacific); details can be found in Appendix F.
- Ethnicity: Hispanic or Latino vs. Not Hispanic or Latino

6.8. Data Safety Monitoring Board

An independent DSMB will periodically review (through regular meetings) blinded and unblinded data, including both safety and cases of respiratory disease through the end of the study. The DSMB will be composed of external independent participant 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.

7. Changes from Planned Analyses in Protocol

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

- Appendix H Estimands and Estimand Specification: Estimands language has been added for primary efficacy endpoints and primary safety endpoints.
- Additional exploratory objectives were added regarding the effect of immunization with mRNA-1345 vaccine on the prevention of RSV-LRTD with shortness of breath and at least one other symptom of lower respiratory tract involvement as well as the combination of hypoxemia and tachypnea (in Section 2.3), along with associated exploratory objectives (in Section 3.3) and analysis plans (in Section 6.3.3), as corollaries to the planned exploratory objective and endpoint regarding RSV-LRTD with at least 1, 2, 3, 4, or 5 symptoms of lower respiratory tract involvement. The selection of shortness of breath as a symptom of interest arose from discussions with RSV experts, including those who contributed to the development of our case definition. The experts advised that shortness of breath is a symptom of severity and can drive participants to seek a higher level of care. Shortness of breath has been included in other published RSV case definitions (Falsey et al, NEJM 2005 and Branche et al, NEJM 2022) in combination with other lower respiratory signs and symptoms. It is also reported across all ages and risk groups. Ongoing work by the mRNA-1345 P301 epidemiologist in conjunction with external experts, working with

an external validation data set, has shown that shortness of breath has good sensitivity and specificity for detecting severe RSV, including RSV-associated hospitalizations (manuscript in preparation). Tachypnea and hypoxemia were selected as objective signs of respiratory distress which might also signal severe respiratory disease.

- Additional exploratory endpoints were added regarding the effect of immunization with mRNA-1345 vaccine to prevent the first hospitalization associated with an RSV positive case. This endpoint is defined without the requirement of investigator's confirmation of RSV-LRTD or RSV-ARD diagnosis, and expands the time window from the RT-PCR positive test result to 28 days in order to account for hospitalization due to delayed sequelae of RSV infection, including exacerbation of underlying respiratory disease (such as exacerbation of chronic lung disease, bacterial suprainfection, or hypoxic respiratory failure) which may result in an associated respiratory SAE, therefore provide an alternative way of evaluate the hospitalization. This exploratory endpoint was added (in Section 2.3), along with an associated exploratory endpoint (in Section 3.3) and analysis plan (in Section 6.3.3).
- An additional exploratory endpoint was added regarding the effect of immunization with mRNA-1345 vaccine to prevent a composite endpoint of either first hospitalization associated with an RSV positive case and/or use of supplemental oxygen (in Section 2.3), along with an associated exploratory endpoint (in Section 3.3) and analysis plan (in Section 6.3.3), as a corollary to the key secondary objective of evaluating the efficacy of mRNA-1345 to prevent 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. This was added because while hospitalization is a key component of the World Health Organization's case definition of Severe Acute Respiratory Infection, used for expanded RSV sentinel surveillance among adults, hospitalization is not the only measure of severe disease, and as shortness of breath is a symptom identified by experts as indicative of severe disease, associated with hospitalization, the progression of shortness of breath to hypoxia requiring oxygen supplementation represents a measure of severe disease. The combination of either hospitalization (as a marker of severity) with requirement of oxygen supplementation (as a marker of likelihood of disease progression) as a composite endpoint is designed to capture a range of participants with severe RSV-associated lower respiratory tract disease.

8. References

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WHO Drug Dictionary (UMC | WHODrug Global (who-umc.org))

World Bank Regions and Income Classifications
(https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)

9. List of Appendices

9.1. Appendix A Standards for Variable Display in Tables, Figures and Listings (TFLs)

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

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

9.2.Appendix B Analysis Visit Windows

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

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

Step 2: If the assessments are collected at an unscheduled visit or early termination visit, the collected data will be mapped using the analysis visit windows described in Table 6 below.

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

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

Table 6: Analysis Visit Windows for Immunogenicity Assessments

Visit	Visit Window in Study Day
Day 1	1
Day 15 (on Phase 2 only)	[12, 18]
Day 29	[22, 43]
Day 181	[167, 195]
Day 365	[351, 379]
Day 546	[532, 560]
Day 730	[716, 744]

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

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

1. Missing or partial medication start date:

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

2. Missing or partial medication stop date:
    a. If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
    b. If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
    c. If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

9.4.Appendix D Imputation Rules for Missing Dates of AEs

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

1. Missing or partial start date:

- If only Day is missing, use the first day of the month, unless:
    - The AE end date is on/after the date of IP injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the IP injection. In this case, use the date of IP injection.
- If Day and Month are both missing, use the first day of the year, unless:

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

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

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

9.5. Appendix E Imputation Rules for Missing Dates of Procedures/Surgeries

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

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

9.6. Appendix F World Bank Regions and Income Classifications

Each country involved in the current trial will be classified for subgroup analyses purposes by region and income level, based on the World Bank classification 2022 (World Bank Country and Lending Groups), as follows:

Table 7: World Bank Income Classifications 2022

World Bank Income Classifications	mRNA-1345-P301 Countries
Low-income economies	-
Lower-middle-income economies	Bangladesh
Upper-middle-income economies	Argentina, Colombia, Costa Rica, Mexico, Panama, South Africa
High-income countries	Australia, Belgium, Canada, Chile, Finland, Germany, Japan, S. Korea, New Zealand, Poland, Puerto Rico, Singapore, Spain, Taiwan, UK, USA

Table 8: World Bank Regions Classifications

World Bank Regions Classifications	mRNA-1345-P301 Countries
East Asia and Pacific	Bangladesh, Japan, Taiwan, South Korea, Singapore, Australia, New Zealand
Europe and Central Asia	UK, Belgium, Germany, Finland, Poland, Spain
Latin America & the Caribbean	Puerto Rico, Mexico, Panama, Argentina, Colombia, Chile, Costa Rica
Middle East and North Africa	-
North America	USA, Canada
South Asia	-
Sub-Saharan Africa	South Africa

9.7.Appendix G Schedule of Events

Table 9: Schedule of Events (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									
Review of eDiary for recording solicited ARs			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
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]							

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 unsolicited AEs		X	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[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 the 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.
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 to document resolution, or return to baseline, of symptoms and to collect information on healthcare usage and concomitant medications through 30 days from the onset or worsening of RSV-like illness, whichever comes first.
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 up to 5 days before the unscheduled visit will 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 10: Schedule of Events (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	

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
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						
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 the 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.

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 to document resolution, or return to baseline, of symptoms and to collect information on healthcare usage and concomitant medications through 30 days from the onset or worsening of RSV-like illness, whichever comes first.
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 up to 5 days before the unscheduled visit will 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.

9.8.Appendix H Estimands and Estimand Specifications

Table 11: Intercurrent Events

Label	Intercurrent Event Type
IcEv1 (early discontinuation or unrelated death)	Early discontinuation from study or unrelated death prior to RT-PCR documented RSV-LRTD.
IcEv2 (early RSV-ARD)	RSV-ARD with start (occurrence) date from Day 1 to Day 14.
IcEv3 (Alternative RSV vaccine)	Use of alternative RSV vaccine.
IcEv4 (Prohibited medications)	Use of prohibited medications deemed to impact on efficacy.

Abbreviation: IcEv: intercurrent event; LRTD: lower respiratory tract disease; RSV: respiratory syncytial virus; RSV-LRTD: respiratory syncytial virus lower respiratory tract disease; RSV-ARD : respiratory syncytial virus acute respiratory disease; RT-PCR: reverse transcription polymerase chain reaction.

Table 12: Summary of Primary Efficacy Estimands with Rationale for Strategies to Address Intercurrent Events

Objective: To demonstrate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection

Estimand Label	Primary Efficacy Estimand 1a (on the PPE Set)	Supportive Efficacy Estimand 1b (on the mITT Set)	Supportive Efficacy Estimand 1c (on the PPE Set)	Supportive Efficacy Estimand 1d (on the PPE Set)
Estimand Description	Vaccine efficacy measured as VE (%) = 100% × (1 – HR) in adults ≥ 60 years old who receive IP administration **without major protocol deviations impacting efficacy**. HR= Hazard Ratio (mRNA-1345 vs. Placebo) of RT-PCR documented RSV-LRTD with onset from 14 days post-injection up to 12 months post-injection.	Vaccine efficacy measured as VE (%) = 100% × (1 – HR) in adults ≥ 60 years old who receive IP administration **irrespective of any major protocol deviations impacting efficacy**. HR= Hazard Ratio (mRNA-1345 vs. Placebo) of RT-PCR documented RSV-LRTD with onset from 14 days post-injection up to 12 months post-injection.	Vaccine efficacy measured as VE (%) = 100% × (1 – **IRR**) in adults ≥ 60 years old who receive IP administration **without major protocol deviations impacting efficacy**. Incidence rate (IR) = number of participants with an event (i.e. the first occurrence of RSV-LRTD at least 14 days after the injection up to 12 months after the injection) divided by the person-time (years). IRR = [IR mRNA-1345] / [IR Placebo].	Vaccine efficacy measured as VE (%) = 100% × (1 – RR) in adults ≥ 60 years old who receive IP administration without major protocol deviations impacting efficacy. RR=Relative risk (mRNA-1345 vs. Placebo) of RT-PCR documented RSV-LRTD with onset from 14 days post-injection up to 12 months post-injection.
Target Population	Adults aged 60 years or older who receive the IP administration, complete at least 1 visit or surveillance contact 14 days after the IP administration, and have no major protocol deviations impacting the efficacy outcomes.	Adults aged 60 years or older who receive the IP administration.	As per Estimand 1a.	As per Estimand 1a.

Endpoint	First occurrence of protocol-defined RSV-LRTD with event onset within the period of 14 days post-injection up to 12 months post-injection. where the surveillance time is from randomization up to onset of event, 12 months or censoring. (see Section 6.3.1.3).	First occurrence of protocol-defined RSV-LRTD with event onset within the period of 14 days post-injection up to 12 months post-injection. where the surveillance time is from randomization up to onset of event, 12 months or censoring. (see Section 6.3.1.3).	As per Estimand 1a.	As per Estimand 1a.
Treatment Conditions	mRNA-1345 (Test) vs. Placebo (Reference)	As per Estimand 1a.	As per Estimand 1a.	As per Estimand 1a.

Population-Level Summary	Vaccine efficacy defined as 100% × (1-HR) where HR = Hazard Ratio (mRNA-1345 vs. Placebo). The HR is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the vaccination group as a fixed effect, adjusting for stratification factors at randomization. The time to the first event is calculated as the time (in days) from randomization to the date of the first event or censoring.	As per Estimand 1a.	Vaccine efficacy defined as 100% × (1-IRR) where IRR = [IR mRNA-1345] / [IR Placebo]. Incidence rate (IR) = number of participants with an event (i.e. the first occurrence of RSV-LRTD at least 14 days after the injection up to 12 months after the injection) divided by the person-time (years). The person-time is calculated as the time (in years) from randomization to the date of the first event for participants with an event, and the time from randomization to the date of censoring for participants without an event.	Vaccine efficacy defined as 100% × (1-RR) where RR = Relative Risk calculated as ratio of cumulative incidences (mRNA-1345 vs. Placebo).
Intercurrent Event Strategy				
IcEv1 (early discontinuation or unrelated death)	Hypothetical	Hypothetical	Hypothetical	Hypothetical
IcEv2 (early RSV-ARD)	Hypothetical	Hypothetical	Hypothetical	Hypothetical
IcEv3 (Alternative RSV vaccine)	Principal stratum	Treatment policy	Principal stratum	Principal stratum

IcEv4 (Prohibited medications)	Principal stratum	Treatment policy	Principal stratum	Principal stratum
Rationale for Strategies	This estimand seeks to understand vaccine efficacy during a surveillance period (14 days to 12 months post-injection) which starts after the vaccine is considered to have stimulated an immune response in adults aged 60 or older who receive the IP administration and comply with key protocol criteria. A principal stratum is used to exclude subjects with major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from such intercurrent events.	A treatment policy strategy is used for evaluating vaccine efficacy including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e. major protocol deviations affecting efficacy). There is interest in understanding efficacy in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The hypothetical strategy is employed for the other intercurrent events which match Estimand 1a.	As per Estimand 1a.	As per Estimand 1a.

Table 13: Summary of Primary Safety Estimands with Rationale for Strategies to Address Intercurrent Events

Objective: To evaluate the safety and tolerability of the mRNA-1345 vaccine			
Estimand Label	**Safety Estimand 2a**	**Safety Estimand 2b**	**Safety Estimand 2c**
Estimand Description	Proportion of participants who would have at least one solicited local or systemic adverse reaction (AR) up to 7 days post-injection. Occurrence of solicited local or systemic ARs during 7 days following IP injection will be considered irrespective of the use of other medications. Similar estimands for local solicited ARs, systemic solicited ARs and specific ARs may be specified.	Proportion of participants who would have at least one unsolicited adverse event (AE) up to 28 days post-injection. Occurrence of unsolicited AEs during 28 days following IP injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.	Proportion of participants who would have at least one unsolicited Medically-attended AEs (MAAEs) up to 24 months post-injection. Occurrence of unsolicited MAAEs during 24 months following IP injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.
Target Population	Adults aged 60 years or older who receive the IP administration and provide solicited ARs data in the first 7 days post-injection.	Adults aged 60 years or older who receive the IP administration.	Same as Estimand 2b.
Endpoint	Incidence of solicited local or systemic ARs in the 7 days following the IP injection.	Incidence of unsolicited AEs in the 28 days following the IP injection.	Incidence of unsolicited MAAEs in the 24 months following the IP injection.
Treatment Conditions	mRNA-1345 (Test) vs. Placebo (Reference)	Same as Estimand 2a.	Same as Estimand 2a.
Population-Level Summary	Proportion of participants who would experience solicited local or systemic ARs within 7 days of IP injection.	Proportion of participants who would experience unsolicited AEs within 28 days of IP injection.	Proportion of participants who would experience unsolicited MAAEs within 24 months of IP injection.
Intercurrent Event Strategy			
IcEv3 (Alternative RSV vaccine)	Treatment Policy	Treatment Policy	Treatment Policy

IcEv4 (Prohibited medications)	Treatment Policy	Treatment Policy	Treatment Policy
Rationale for Strategies	Count all relevant safety events observed, irrespective of the use of other medications.		
Estimand Label	**Safety Estimand 2d**	**Safety Estimand 2e**	**Safety Estimand 2f**
Estimand Description	Proportion of participants who would have at least one unsolicited adverse event of Special Interest (AESI) up to 24 months post-injection. Occurrence of unsolicited AESI during 24 months following IP injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.	Proportion of participants who would have at least one unsolicited serious adverse event (SAE) up to 24 months post-injection. Occurrence of unsolicited SAEs during 24 months following IP injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.	Proportion of participants who would have at least one AE leading to study discontinuation up to 24 months post-injection. Occurrence of unsolicited AEs leading to study discontinuation during 24 months following IP injection will be considered irrespective of the use of other medications. Similar estimands for specific PTs and SOCs may be specified.
Target Population	Same as Estimand 2b.	Same as Estimand 2b.	Same as Estimand 2b.
Endpoint	Incidence of unsolicited AESI in the 24 months following the IP injection.	Incidence of unsolicited SAEs in the 24 months following the IP injection.	Incidence of unsolicited AEs leading to study discontinuation in the 24 months following the IP injection.
Treatment Conditions	Same as Estimand 2a.	Same as Estimand 2a.	Same as Estimand 2a.
Population-Level Summary	Proportion of participants who would experience unsolicited AESI within 24 months of IP injection.	Proportion of participants who would experience unsolicited SAEs within 24 months of IP injection.	Proportion of participants who would experience unsolicited AEs leading to study discontinuation within 24 months of IP injection.
Intercurrent Event Strategy			
IcEv3 (Alternative RSV vaccine)	Treatment Policy	Treatment Policy	Treatment Policy

IcEv4 (Prohibited medications)	Treatment Policy	Treatment Policy	Treatment Policy
Rationale for Strategies	Count all relevant safety events observed, irrespective of the use of other medications.		

9.9. Appendix I Adverse Events of Special Interest

Table 14: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150 × 109 cells per liter • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
New onset of or worsening of neurologic diseases	Neurologic diseases include the following: • Guillain-Barré Syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per-protocol Section 8.3.3.1 • Follow the reporting procedures in protocol Section 8.3.10
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

9.10. Appendix J Definition of TEAE of Special Interest by SMQ

Table 15: TEAE of Clinical Interest by SMQ

SMQ	Broad/Narrow Search	SMQ Search Criteria
Anaphylactic Reaction	Broad/Narrow	Specified PT terms and algorithmic approach specified in Table 16
Angioedema	Broad/Narrow	Specific PT terms
Cardiac Arrhythmias	Broad/Narrow	Specific PT terms
Cardiac Failure	Broad/Narrow	Specific PT terms
Cardiomyopathy	Broad/Narrow	Specific PT terms
Central Nervous System Vascular Disorders	Broad/Narrow	Specific PT terms
Convulsions	Broad/Narrow	Specific PT terms
Demyelination	Broad/Narrow	Specific PT terms
Embolic and Thrombotic Events	Broad/Narrow	Specific PT terms
Guillain-Barre Syndrome	Broad/Narrow	Specific PT terms
Haematopoietic Cytopenias	Broad/Narrow	Specific PT terms
Hypersensitivity	Broad/Narrow	Specific PT terms
Immune-mediated/Autoimmune Disorders	Broad/Narrow	Specific PT terms
Ischemic Heart Disease	Broad/Narrow	Specific PT terms
Noninfectious Myocarditis/Pericarditis	Broad/Narrow	Specific PT terms
Peripheral Neuropathy	Broad/Narrow	Specific PT terms
Vasculitis	Broad/Narrow	Specific PT terms

Table 16: Algorithmic Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

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

- A term from Category D (Cardiovascular/Hypotension) and at least one of the following:
  - A term from Category B (Upper Airway/Respiratory) that occurred within 24 hours of each other.
  - A term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.

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

B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
B	Broad	Nasal obstruction
B	Broad	Oedema mouth
B	Broad	Oropharyngeal oedema
B	Broad	Oropharyngeal spasm
B	Broad	Oropharyngeal swelling
B	Broad	Pharyngeal oedema
B	Broad	Pharyngeal swelling
B	Broad	Respiratory arrest
B	Broad	Respiratory distress
B	Broad	Respiratory failure
B	Broad	Reversible airways obstruction
B	Broad	Sensation of foreign body
B	Broad	Sneezing
B	Broad	Stridor
B	Broad	Swollen tongue
B	Broad	Tachypnoea
B	Broad	Throat tightness
B	Broad	Tongue oedema
B	Broad	Tracheal obstruction
B	Broad	Tracheal oedema
B	Broad	Upper airway obstruction
B	Broad	Vaccine associated enhanced respiratory disease
B	Broad	Wheezing
C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling
C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria

C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest
D	Broad	Cardiovascular insufficiency
D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension

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

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

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

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTX, Inc.**
Protocol Number:	**mRNA-1345-P301**

Document Description:	Statistical Analysis Plan
SAP 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
SAP Version Number:	Version 2.0
Effective Date:	31MAY2023

Author(s):

For PPD: (Name), Biostatistician II

Approved by:

PPD

31-May-2023

(DD-MMM-YYYY)

ModernaTX, Inc.

PPD

31-May-2023

(DD-MMM-YYYY)

ModernaTX, Inc.

Statistical Analysis Plan (SAP) Client Approval Form

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