24 July 2025
EMADOC-1700519818-2305287
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000248175

Invented name: mRESVIA

International non-proprietary name: Respiratory syncytial virus mRNA vaccine (nucleoside modified)

Note
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACIP	Advisory Committee on Immunization Practices
ADEM	acute demyelinating encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARD	acute respiratory disease
AU	arbitrary units
bAb	binding antibody(ies)
BMI	body mass index
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Case fatality rate
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CMC	Chemistry, Manufacturing, and Controls
CMQ	Customized MedDRA Query
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CSR	clinical study report
DBL	database lock
DCO	data cutoff
DM	diabetes mellitus
DSMB	data safety monitoring board
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicines Agency
EOS	end of study
ESRD	end-stage renal disease
EU	European Union
FDA	United States Food and Drug Administration
GBS	Guillain-Barré Syndrome
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
HCP	healthcare provider
HLGT	high level group term
hMPV	human metapneumovirus
H0	null hypothesis
HR	high risk
IA	interim analysis
IP	investigational product
IM	intramuscular
IU	international units
LB	lower bound
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LRTD	lower respiratory tract disease
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent-to-treat
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody(ies)
NI	noninferiority
NIH	National Institutes of Health
NPA	National Prescription Audit
PP	per-protocol
PPE	Per-protocol Efficacy
PPI	per-protocol immunogenicity
PostF	Postfusion
PreF	Prefusion
PT	preferred term
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RSV-A	RSV subtype A
RSV-B	RSV subtype B
RSV-ARD	respiratory syncytial virus-associated acute respiratory disease
RSV-LRTD	respiratory syncytial virus-associated lower respiratory tract disease
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCDM	shared clinical decision-making
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
SRR	seroresponse rate
Study P101	Study mRNA-1345-P101
Study P301	Study mRNA-1345-P301
Study P303	Study mRNA-1345-P303
Th1	T helper type 1
Th2	T helper type 2
US	United States
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biologic Products Advisory Committee
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain S.L. submitted to the European Medicines Agency on 30 January 2025 an application for a variation:

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

The MAH proposes an extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV for mRESVIA, based on results from Study mRNA-1345-P303 (Part A) - A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults. As a consequence, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC and the corresponding sections of the Package Leaflet are updated accordingly. The updated RMP Version 1.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI.

In this context, the requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

The PDCO issued an opinion on compliance for the PIP study 1 mRNA-1345-P101 for PIP P/0195/2023.

Information relating to orphan market exclusivity and similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller Berghaus

Timetable	Actual dates
Submission date	05 February 2025
Start of procedure:	22 February 2025
CHMP Rapporteur's preliminary assessment report circulated on:	28 April 2025
PRAC RMP advice and assessment overview adopted by PRAC	08 May 2025
Joint Rapporteur's updated assessment report circulated on:	16 May 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	12 May 2025
MAH's responses submitted to the CHMP on:	23 May 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	02 July 2025
PRAC RMP advice and assessment overview adopted by PRAC	10 July 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	17 July 2025
CHMP Opinion	24 July 2025

2. Scientific discussion

2.1. Introduction

mRESVIA (mRNA-1345) is an approved RSV vaccine indicated for active immunization for the prevention of RSV-LRTD in individuals 60 years and older. A single injection of 50 µg of mRESVIA demonstrated an efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms and 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms (mRESVIA Product Information).

To expand the indication to adults ≥18 to ≤59 years of age considered at increased risk for RSV-LRTD, the Study mRNA-1345-P303 (P303) Part A was designed to evaluate safety and effectiveness of mRNA-1345 in this population of adults.

2.1.1. Problem statement

2.1.2. About the product

mRNA Platform

mRNA-1345 is comprised of a single mRNA sequence that encodes the RSV F glycoprotein stabilized in the preF conformation formulated in a mixture of 4 lipids: SM-102, mPEG2000-DMG, DSPC, and cholesterol to form an RNA-lipid complex (LNP).

The MAH's mRNA-based vaccine platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express encoded antigens. The delivered mRNA does

not enter the cellular nucleus, does not interact with the genome, is nonreplicating, is expressed transiently, and does not persist in the body. To protect mRNA from rapid degradation in plasma and serum by ribonucleases and to aid in mRNA uptake by cells, mRNA is encapsulated and delivered to the target cell within a proprietary LNP.

The precision and standardization of the mRNA vaccine platform enables efficient manufacturing scale-up of safe and effective vaccines without reliance on processes and substrates that are specific to each pathogen.

mRNA-1345 Formulation

The MAH intends to use the same strength (50 µg), formulation and presentation as the currently approved mRESVIA product).

mRNA-1345 injection is an LNP dispersion that contains an mRNA encoding for the RSV F glycoprotein stabilized in the preF conformation. The general structure of mRNA-1345 was previously described in the original application. The mRNA is encapsulated in a mixture of 4 lipids common to the MAH's mRNA vaccine platform: SM-102 (a custom-manufactured, proprietary ionizable lipid), mPEG2000-DMG, DSPC, and cholesterol.

mRNA-1345 Mechanism of Action

RSV, a member of the Pneumoviridae family has a single serotype and 2 subtypes, RSV-A and RSV-B. RSV-A and RSV-B subtypes are differentiated based on the sequence of the attached glycoprotein G. The F glycoprotein is highly conserved between subtypes, with amino acid sequence identities of approximately 90%, and is the major target of nAbs.

mRNA-1345 is an LNP-encapsulated mRNA-based vaccine encoding the membrane-anchored RSV F glycoprotein, derived from an RSV-A strain (RSV-A A2 strain), and stabilized in the preF conformation. The F glycoprotein exists in 2 primary conformational states: preF and postF. The preF state facilitates entry into the host cell through a conformational change to the postF state. The preF conformation was selected because it displays all the epitopes known to elicit nAb and is the primary target of the nAb response following RSV exposure.

The mRNA-1345 vaccine is delivered via IM injection. The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of intramuscular vaccines and distribution via the lymphatic system. mRNA does not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and the spleen, in which the average half-life values ranged from 14.9 to 63.0 hours in Sprague Dawley rats. After delivery into cells, the mRNA utilizes the cell's translational machinery to produce the RSV F protein in the preF conformation, which after proper assembly and processing is trafficked to the cell membrane.

mRNA-1345 stimulates innate and adaptive immune responses, resulting in secretion of antibodies that neutralize RSV-A and RSV-B subtypes and induction of RSV F-specific Th1-biased CD4+ T cells, as well as CD8+ T cells.

2.1.3. About the Disease or condition

Overview of RSV in Adults with Risk Factors

RSV is a significant cause of respiratory illness, particularly in adults with certain comorbid medical conditions. These conditions include chronic lung diseases such as COPD and asthma, and chronic heart diseases like CHF and CAD. Studies over the past 2 decades have solidified RSV as a critical

pathogen among these populations, contributing to severe respiratory complications.

Comorbid Risk Factors for Severe RSV in Adults

While older adults have historically been a focus of RSV prevention efforts, emerging data highlight that younger adults 18 to 59 years of age with certain comorbidities also face a significant disease burden. A global systematic review found that the frequency of severe outcomes from RSV disease among younger adults with comorbidities was generally similar to that experienced by older adults, suggesting the importance of chronic conditions in elevating risk.

A recent study using a large US health claims database found that among adults with risk factors for severe influenza (as defined by the CDC), the incidence of RSV hospitalization was elevated in those 18 to 49 years (26 times higher) and 50 to 64 years (36 times higher) compared to similarly aged adults without these risk factors.

Similarly, measuring the incidence of RSV-associated hospitalization in adults with and without specific risk factors demonstrates the influence of these conditions on RSV disease severity. In a prospective, population-based, active surveillance study conducted in Rochester and New York City, NY, across multiple RSV seasons, the presence of CHF, CAD, COPD, or DM increased the incidence of RSV-associated hospitalization by a median of 5-fold in younger adults, with an increase as high as 33-fold in adults 20 to 39 years with CHF. A joint analysis of published literature and hospitalization data from Canada concluded that the risk of severe outcomes associated with RSV increases with the presence of comorbidities in adults. These findings underscore considerable impact of comorbid conditions on RSV severity in younger adults.

Furthermore, the June 2024 ACIP meeting additionally identified asthma, severe obesity, liver conditions, later stage CKD, and recent history of cancer as conditions increasing the risk of severe RSV disease in younger adults 50 to 59 years. Consistent with US studies and the CDC, the EU CDC describes diabetes, heart disease, and lung disease as important RSV risk factors.

In a retrospective study using registry and virologic surveillance data in adults ≥45 years in Denmark and Scotland, adults 45 to 54 years and 55 to 64 years with COPD, asthma, ischemic heart disease, stroke, DM, or CKD had up to 8-fold and 7-fold increases in RSV-associated hospitalizations, respectively, compared to adults in the same age range in the general population. In a retrospective cohort study conducted in Israel over multiple seasons, chronic pulmonary diseases, cardiovascular diseases, chronic renal failure, hypertension, and DM increased the risk of RSV hospitalization by approximately 2- to 4-fold when adjusting for age in adults ≥18 years. A population-based surveillance study conducted in New Zealand linking RSV hospitalizations to national administrative data found that across all ages, RSV hospitalization rates were significantly higher among adults with COPD, asthma, CHF, and CAD compared with those without each corresponding condition.

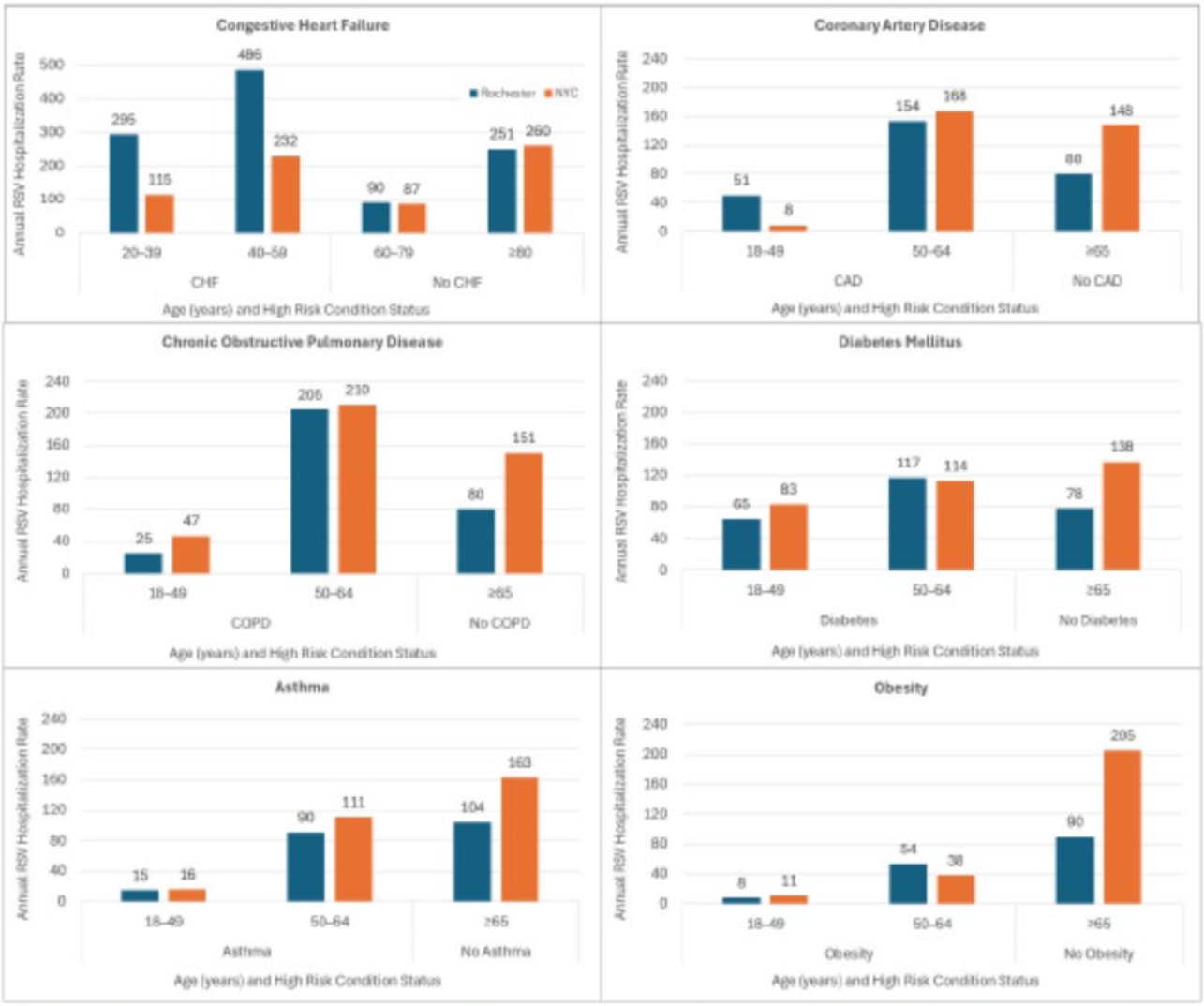
Burden of RSV-Associated Hospitalizations and Deaths in Adults with Risk Factors

RSV vaccines have been approved and recommended for use in the 60 year and older age group. Review of the burden of disease in younger adults (18 to 59 years) establishes a similar importance of disease and RSV hospitalization in this younger group compared to the older group.

In the study by Branche et al (2022), the incidence of RSV-associated hospitalization in younger adults with certain risk factors is similar or higher than for older adults without the same risk factors (Figure 1). Although formal statistical comparisons were not performed, younger adults 50 to 64 years with CAD and COPD had a higher incidence of RSV-associated hospitalization than older adults ≥65 years without these risk factors. In addition, at the Rochester site, younger adults 18 to 49 years and 50 to 64 years with DM or asthma had a similar incidence of RSV hospitalization as older adults ≥65 years without DM or asthma. The incidence of RSV hospitalization in younger adults with CAD,

CHF, COPD, DM, or asthma ranged from 7.8 per 100,000 persons in adults 18 to 49 years with CAD to 485.8 per 100,000 persons in adults 40 to 59 years with CHF.

Figure 1: Incidence Rate of RSV Hospitalization Per 100,000 Adults by Age Group and Medical Condition



Abbreviations: CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NYC = New York City; RSV = respiratory syncytial virus.

Rates rounded to the nearest whole number

Source: Adapted from Branche et al 2022

Additionally, a global meta-analysis demonstrated that the case fatality ratio in high-risk adults hospitalized with RSV varies and can be substantial, depending on patient characteristics and geography. Specifically, the case fatality ratio in RSV patients with cardiopulmonary disease was estimated at 10.1% (95% CI: 6.5–17.6%). In a prospective study enrolling adults ≥18 years admitted to the hospital with acute respiratory infection, 31% of laboratory-confirmed RSV hospitalizations with mechanical ventilation and/or death were among those under 60 years. In this study, the frequency of severe RSV hospitalization outcomes was similar to those for COVID-19 and influenza among unvaccinated individuals, including the risk of mechanical ventilation and/or in-hospital death among adults ≥18 years; restricting the population to adults ≥60 years (62% of the adults enrolled) revealed similar results, suggesting consistency in the findings across the entire adult life course. In a German hospital database study, among adults 18 to 59 years hospitalized with RSV-coded disease,

of whom 42.0% had underlying circulatory disease, 35.7% had an immune disorder, 14.3% had diabetes, and bacterial pneumonia more commonly developed in younger adults (10.5%) than in the paediatric (2.0%) and older adult participants (7.1%). The median length of hospital stay in adults 18 to 59 years was similar to that in adults ≥60 years (7 vs 8 days). Additionally, severity of outcomes related to RSV does not appear to be associated with one RSV subgroup (A or B), which co-circulate globally; this includes no identified differences in adults.

Cardiac and Cardiopulmonary Complications Associated with RSV

RSV infections frequently contribute to acute cardiac events, particularly in adults with pre-existing cardiovascular disease. Data from the US RSV Hospitalization Surveillance Network spanning 5 seasons revealed that approximately one-quarter of hospitalized adults aged ≥50 years with RSV experienced an acute cardiac event. This study demonstrated how the presence of cardiovascular risk factors, irrespective of certain age groups (eg, 50 to 64 years vs 65 to 74 years), can be important determinants of acute cardiac events associated with RSV. Additionally, the MAH's analysis of a large US health claims database estimated that RSV accounted for 3.1% to 5.5% of all cardiorespiratory hospitalizations among adults >18 years, increasing to 5.9% to 6.4% in high-risk adults which included persons with asthma, COPD, heart failure, CAD, DM, advanced liver disease, CKD/ESRD, and immunocompromise. This underscores the substantial burden of RSV on cardiac health, particularly in adults with pre-existing conditions.

Unmet Medical Need

The first RSV vaccines were developed and authorized to prevent RSV-LRTD in adults aged 60 years and older. The risk of RSV-associated hospitalization in adults 18 to 59 years with certain comorbid medical conditions is comparable to that in older adults without these conditions, highlighting the need for additional vaccine options. Because no approved drugs are currently available to treat RSV, introducing additional vaccine options to prevent RSV-LRTD in adults 18 to 59 years with risk factors remains an important public health need.

Therapeutic Rationale Supporting Investigation

The approvals of mRESVIA (mRNA-1345) for adults ≥60 years were based on the demonstration of clinical efficacy against RSV-LRTD, tolerability, and the safety profile evaluated in over 36,000 participants. A total of approximately 30% of participants in this pivotal study had underlying medical conditions leading to increased risk of RSV-LRTD. Study P303 was designed to assess the safety, reactogenicity, and immunogenicity of mRNA-1345 in adults ≥18 to ≤59 years with chronic conditions including CHF, COPD, asthma, CAD, or DM. The effectiveness of a single dose of 50 µg mRNA-1345 was inferred following the demonstration of noninferiority of induced nAb levels in this younger population compared to nAb levels measured in the older participants in Study P303. These data and approvals, especially when considered with the burden of disease and unmet medical need, lay the groundwork for expanding the mRNA-1345 use to younger adults (18 to 59 years) with conditions placing them at increased risk for RSV-LRTD.

The burden of RSV disease in adults between 18 and 59 years at increased risk for RSV-LRTD – as described above - warrants access to RSV vaccination. Data summarized in this submission confirm that mRNA-1345 is anticipated to prevent RSV-LRTD in this younger population, establishing mRNA-1345 (50 µg) as an RSV vaccine for use throughout adulthood.

Both natural and vaccine-induced immunity to RSV wane over time, and as such, adults may benefit from revaccination following primary inoculation. Revaccination of adults with mRNA-1345 12 months after primary vaccination restored nAb levels to those obtained following primary vaccination. Given that adults ≥18 to ≤59 years at increased risk for RSV-LRTD are likely to experience

repeated exposures to RSV as they age, revaccination may be essential to maintaining protection over time.

2.1.4. The development programme /compliance with CHMP guidance/scientific advice

The MAH did not obtain scientific advice specific to this variation application.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable to the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The mRNA-1345 clinical development program initiated with the first-in-human Phase 1 study mRNA 1345-P101 (Study P101), designed to guide selection of dose and regimen to advance to the larger, pivotal, Phase 2/3 clinical safety and efficacy study mRNA-1345-P301 (Study P301). In Study P301, over 18,000 participants ≥60 years of age were administered at least 1 dose of 50 µg mRNA-1345. This study demonstrated that a single injection of 50 µg of mRNA-1345 has an efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms and 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms (mRESVIA Product Information). These studies demonstrated that mRNA-1345 had acceptable tolerability and safety and supported the approval of mRNA-1345 for use in older adults.

This submission summarizes data from the Phase 3 Study P303, evaluating tolerability, safety and immunogenicity of mRNA-1345 in adults ≥18 to ≤59 years of age at increased risk for RSV-LRTD.

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number (Country)	**Study Design**	**Study Population**	**Regimen**	**Number of Participants Exposed**	**Immunogenicity Objectives Included in the Application**
mRNA-1345-P303 (US, Canada, UK)	Phase 3, partly randomized, observer-blind pivotal safety and immunogenicity study	High-risk adults <60 years, including adults with underlying comorbidities (cardiac, lung, or metabolic disease)	Single IM injection: mRNA-1345 30 or 50 µg 1:1 randomization	mRNA-1345 30 µg (497) mRNA-1345 50 µg (502)	Evaluate the immune response to RSV-A and RSV-B nAbs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3

Study Number (Country)	Study Design	Study Population	Regimen	Number of Participants Exposed	Immunogenicity Objectives Included in the Application
					efficacy study (mRNA-1345-P301).
mRNA1345P301	Phase 2/3, randomized, observer-blind, placebo-controlled pivotal safety, tolerability, and efficacy study	Adults ≥60 years	Single IM injection mRNA-1345 50 µg or placebo 1:1 randomization	mRNA-1345 50 µg (18231) Placebo (18181)	Used as a comparison group for immunobridging for Study mRNA1345-P303.

2.4. Clinical efficacy

2.4.1. Main study(ies)

mRNA-1345-P303 (US, Canada, UK) - Phase 3, partly randomized, observer-blind pivotal safety and immunogenicity study

Methods

The submission summarizes data from the Phase 3 Study P303, evaluating tolerability, safety and immunogenicity of mRNA-1345 in adults ≥18 to ≤59 years of age at increased risk for RSV-LRTD. Immunogenicity and safety results are summarized for 502 participants who received 50 µg mRNA-1345 as of 18 Sep 2024, at which time all ongoing participants in Part A had completed at least 180 days of follow-up. Data demonstrate that mRNA-1345 was well-tolerated among younger adults without identification of new safety findings to alter the existing safety profile of mRNA-1345 in adults ≥60 years old. Further, co-primary immunogenicity endpoints were successfully met, supporting the inference of effectiveness (via immunobridging) of a single 50 µg dose in this population.

Completed Clinical Studies

As of 29 November 2024, the data cutoff for the most recent PBRER, there are no completed mRNA-1345 studies; all are ongoing.

Ongoing Studies

This application includes new data from 1 ongoing study. Study P303 is a Phase 3 study designed to evaluate the immunogenicity and safety of mRNA-1345 and comprises 2 parts: Part A (in adults at increased risk for LRTD caused by RSV) and Part B (in immunocompromised adult solid organ transplant recipients). Only Part A of the study is included in this submission. Part A is a Phase 3, randomized, double-blind study to evaluate mRNA-1345 in adults, ≥18 to ≤59 years of age, randomized 1:1 to receive a single dose of 30 or 50 µg of mRNA-1345.

Study P301 is an ongoing Phase 2/3, randomized, observer-blind, placebo-controlled, pivotal efficacy study to evaluate the safety, tolerability, and efficacy of the mRNA-1345 vaccine compared with placebo in adults ≥60 years of age. Data from this study were the basis for initial regulatory approvals of mRESVIA in adults ≥60 years. Immunogenicity data from Study P301 are included in this submission as the basis to assess the immune response to RSV-A and RSV-B after a single dose of 50

µg mRNA-1345 in Study P303. Specifically, nAb GMT at Day 29 against both RSV-A and RSV-B from Study P303 are compared to those in P301 (hypothesis testing).

Study mRNA-1345-P303

Study P303 is an ongoing Phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of mRNA-1345 in adults ≥18 to ≤59 years at increased risk for LTRD. Effectiveness of mRNA-1345 in this population is inferred based on immunobridging nAb levels at Day 29 to those observed in the pivotal P301 clinical efficacy study conducted in adults ≥60 years of age. The study's primary objectives include the evaluation of safety as well as immunogenicity. This submission summarizes results of P303 Part A.

Study P303 was conducted in the US, Canada, and the United Kingdom. Adults who had documented confirmation of at least one of the following conditions were enrolled: CAD and/or CHF, chronic lung disease (including but not limited to COPD or persistent asthma), or Type 1 or Type 2 DM controlled with at least 1 medication. Participants with more than one of these conditions were enrolled. Each participant was assigned a primary risk factor based on the clinical judgment of the Investigator. Enrollment was structured to achieve an approximate distribution of 30% of participants with CAD/CHF, 30% with chronic lung diseases, and 40% with DM as the primary risk factor. Participants were randomized into each dose group according to their primary risk factor, ensuring a similar representation of these high-risk conditions across both groups. A total of 1003 participants were randomized, with 501 participants randomized to the mRNA-1345 50 µg group (hereafter referred to as the 50 µg group) and 502 participants randomized to the mRNA-1345 30 µg group (hereafter referred to as the 30 µg group).

The co-primary immunogenicity objectives of Study P303 were to evaluate nAb responses (to RSV-A and RSV-B) after a single dose of 50 µg mRNA-1345, the same dose approved for mRESVIA in adults ≥60 years of age, using the geometric mean ratio (GMR) as the key measure. NI of nAb levels at Day 29 (for RSV-A and RSV-B) for the P303 (PP Set) 50 µg group were compared to those of the P301 PPI Set. NI was successfully met – and effectiveness was inferred - if the LB of the 95% CI of the GMR was >0.667. Comparison of SRR for the P303 50 µg PP Set and the P301 PPI Set (SRR difference) was evaluated as a secondary objective: NI criteria was met if the LB of the 95% CI of the SRR difference >-10%. Immune responses to the 30 µg dose were assessed as secondary objectives.

The primary safety objective was to evaluate the safety and tolerability of mRNA-1345, including the incidence of solicited local and systemic AR (through 7 days), unsolicited AE (through 28 days), MAAE (through 181 days), and AESIs, SAEs, and AEs leading to discontinuation (until EOS).

Immunogenicity results showed that administration of 50 µg of mRNA-1345 to adults ≥18 to ≤59 years at increased risk for RSV-LRTD induced nAb responses at Day 29 to RSV-A and RSV-B that were NI to those measured in Study P301, meeting the co-primary and secondary objectives for the 50 µg group. Secondary immunogenicity objectives evaluating NI of the 30 µg group also met NI criteria.

mRNA-1345 was well-tolerated in adults ≥18 to ≤59 years at increased risk for RSV-LRTD: most solicited AR were reported as mild or moderate in severity, with onset within 1 to 2 days post-injection and resolution within 3 days. No safety concerns were identified during the study to alter the profile observed in the large P301 study in older adults ≥60 years old.

The study design is presented in the protocol (Study P303 CSR [Appendix 16.1.1]). Study results as of the DCO date of 18 Sep 2024 are summarized in the Study P303 CSR with immunogenicity results in Section 6 and safety results in Section 7. The study is ongoing with continued follow-up for long-term safety and immunogenicity assessments.

Study mRNA-1345-P301

Study P301 is a pivotal, Phase 2/3 randomized, observer-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of mRNA-1345 in adults aged ≥60 years. Participants were randomized 1:1 to receive a single dose of 50 µg mRNA-1345 or placebo, and the study was stratified by age (60 to 74 years vs ≥75 years) and the presence or absence of CHF and/or COPD to ensure balanced representation of populations at increased risk for RSV-LRTD.

The study had 2 primary objectives: to evaluate the efficacy of mRNA-1345 in preventing the first episode of RSV-LRTD with ≥2 and with ≥3 symptoms, and to assess the safety and tolerability of the vaccine. Secondary objectives included evaluating VE against RSV-ARD and by RSV subtype, and evaluating mRNA-1345 induced immune responses.

The Primary Analysis of efficacy, conducted when at least 50% of the total planned RSV-LRTD cases had accrued (DCO 30 Nov 2022), was 83.7% (95.88% CI: 66.0, 92.2) and 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥2 and ≥3 symptoms, respectively. Clinical efficacy of mRNA-1345 against RSV LRTD was successfully demonstrated in that the VE against both efficacy endpoints met the prespecified success criteria of LB of the VE 95% CI >20% (mRESVIA Product Information).

Additional analyses of efficacy were performed after a median of 8.6 months of follow-up (range 15 to 530 days; DCO 30 Apr 2023) when 94.3% of participants had reached at least 6 months of follow-up after injection, with results continuing to meet the prespecified VE success criterion (LB of the VE 95% CI >20%). VE was 63.3% (95% CI: 48.7, 73.7) against RSV-LRTD with ≥2 symptoms and 63.0% (95% CI: 37.3, 78.2) against RSV-LRTD with ≥3 symptoms (mRESVIA Product Information).

Study P301 immunogenicity data are summarized in this submission to support immunobridging to the Study P303 population. The immunogenicity of mRNA-1345 was assessed in the PPI Set of Study P301, which included participants in the 50 µg group who met the PPI Set requirements (including having both pre- and post-injection immunogenicity results).

This submission is supported by the extensive safety database from Study P301. The P301 Safety Set included a total of 36,412 participants (N = 18,231 mRNA-1345; N = 18,181 placebo) and the study continues to follow participants for up to 24 months post-injection. The median duration of safety follow-up was 257 days (range: 1 to 530 days) (DCO 30 Apr 2023), and 93.9% of participants had at least 6 months of follow-up after injection. mRNA-1345 was well-tolerated with no major safety concerns identified in adults' population aged ≥60 years.

Dose Selection

The MAH claims that data summarized in this submission demonstrate that administration of 50 µg of mRNA-1345 to adults between ≥18 to ≤59 years at increased risk for RSV-LRTD satisfied the co-primary immunogenicity objectives. Data show this dose was well-tolerated with the most solicited AR reported as mild to moderate in severity with resolution within 3 days. Safety data are viewed in the context of the large safety database available from the P301 clinical study conducted in adults ≥60 years of age (N = 36,412 in Safety Set).

In addition to meeting co-primary immunogenicity objectives and demonstrating an acceptable tolerability profile, the use of a 50 µg dose of mRNA-1345 in adults ≥18 to ≤59 years at increased risk for RSV-LRTD provides consistency with the currently approved dose for adults ≥60 years.

Indication and Posology

mRESVIA is intended for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults ≥18 to ≤59 years at increased risk of LRTD caused by RSV.

mRNA-1345 is an injectable suspension administered IM as a single 50 µg dose (0.5 mL).

The rationale for development of mRNA-1345 for the adult population with comorbidities with increased risk for RSV-LRTD is acceptable to the CHMP.

Methods, Objectives and Results

The MAH claims that immunogenicity results as of the DCO (18 Sep 2024) demonstrate that co-primary immunogenicity objectives were successfully met (NI of nAb of 50 µg mRNA-1345 in Study P303 PP Set compared to that of the Study P301 PPI Set). By meeting prespecified NI success criteria (ie, LB of the 95% CI of GMR >0.667), data support the inference of effectiveness of mRNA-1345 in adults ≥18 to ≤59 at increased risk for RSV-LRTD.

Immunobridging by demonstration of non-inferiority in terms of the ratio of GM titres in the age group 18-59 yoa as compared to the age group ≥60 yoa from study P301 is acceptable to the CHMP.

The section summarizes results first for the co-primary immunogenicity endpoints (RSV-A and RSV-B nAb GMR at Day 29), observed nAb responses at Day 29, and nAb responses by study subgroups. Responses by age subgroup include a posthoc comparison to an age subset of the Study P301 PPI Set (60 to 69 years).

Participant Population

This section summarizes Baseline characteristics of participants in the P303 mRNA-1345 50 µg group and the total study population (mRNA-1345 50 µg and 30 µg). Baseline characteristics of participants in P301 are briefly presented for the PPI Set.

Study mRNA-1345-P303

In Study P303, a total of 1003 participants were randomized, 501 to the 50 µg group and 502 to the 30 µg group (Study P303 CSR Section 5.1). The PP Set was the primary population used for immunogenicity analyses. This analysis set includes all participants in the FAS who receive the assigned injection dose according to the protocol, had both Baseline (prior to study injection) and at least one post-injection immunogenicity assessment in the protocol-defined window, and had no significant protocol deviations influencing immune response. The 50 µg group PP Set included a total of 494/501 (98.6%) participants.

The Safety Set Includes all participants who received any study injection and was used for all safety analyses. A total of 502 participants were included in the 50 µg group and 497 participants were included in the in the 30 µg group. Participants were included in the study intervention group corresponding to the injection they actually received. One participant who was randomized to receive 30 µg of mRNA-1345 erroneously received a 50 µg dose; this accounts for the higher number of participants (n=502) in the 50 µg Safety Set than in the 50 µg Randomization Set (n=501). Of note, this participant was excluded from the PP Set (as did not receive the assigned dose).

In the 50 µg group (Safety Set), the median age was 53.0 (range 19 to 59) years with similar representation of males and females. Most participants in this group were White (401/502 [79.9%]) and not of Hispanic or Latino ethnicity (360/502 [71.7%]) (Table 1).

Participants in Study P303 were required to have at least one of the prespecified conditions known to increase the risk of RSV-LRTD, including CAD, CHF, chronic lung disease, and DM (Table 1). Participants could have more than one risk factor – all reported conditions were captured and are

reflected in Table 1. Analyses of immune responses by risk factor subgroups utilized the subgroups summarized below. In addition, the number (%) of participants in the risk group are presented: these are the categories to which Investigators assigned each participant, used for purposes of dose randomization.

Type 1 or 2 DM was reported in 299/502 (59.6%) participants, persistent asthma in 195/502 (38.8%), CAD was reported in 104/502 (20.7%) participants, COPD in 52/502 (10.4%), CHF in 45/502 (9.0%), chronic respiratory disease in 12/502 (2.4%), and pulmonary fibrosis in 1/502 (0.2%) participants. Notably, 149/502 (29.7%) participants had at least 2 of these risk factors and 41/502 (8.2%) had at least 3 of these risk factors.

All medical history was captured. All participants in this group reported at least one general medical history event, with the most prevalent conditions (≥20% of participants) being Type 2 DM in 252/502 (50.2%) participants, hypertension in 207/502 (41.2%), asthma in 198/502 (39.4%), obesity in 169/502 (33.7%), gastroesophageal reflux disease in 149/502 (29.7%), depression in 125/502 (24.9%), seasonal allergies in 112/502 (22.3%), anxiety in 112/502 (22.3%), and hyperlipidemia in 106/502 (21.1%) participants (refer to Module 2.7.4 Section 1.2.2, data not presented here).

Obesity was documented in medical history based on Investigator discretion, leading to the discrepancy between BMI values calculated at Day 1 and the diagnosis of obesity recorded in the medical history. A BMI of 30 kg/m² or higher was reported in 319/502 (63.5%) participants in the 50 µg group (Table 1).

Table 1: Baseline Demographics and Characteristics Study P303 (Safety Set)

	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Age (years)			
n	497	502	999
Mean (SD)	49.1 (9.09)	49.6 (9.16)	49.3 (9.12)
Median	52.0	53.0	52.0
Min, Max	19, 59	19, 59	19, 59
Age group 1, n (%)			
18 to 49 years	196 (39.4)	196 (39.0)	392 (39.2)
50 to 59 years	301 (60.6)	306 (61.0)	607 (60.8)
Age group 2, n (%)			
18 to 29 years	19 (3.8)	26 (5.2)	45 (4.5)
30 to 39 years	62 (12.5)	47 (9.4)	109 (10.9)
40 to 49 years	115 (23.1)	123 (24.5)	238 (23.8)
50 to 59 years	301 (60.6)	306 (61.0)	607 (60.8)
Sex, n (%)			
Male	240 (48.3)	233 (46.4)	473 (47.3)

	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Female	257 (51.7)	269 (53.6)	526 (52.7)
Race, n (%)			
White	383 (77.1)	401 (79.9)	784 (78.5)
Black or African American	92 (18.5)	85 (16.9)	177 (17.7)
Asian	13 (2.6)	4 (0.8)	17 (1.7)
American Indian or Alaska Native	3 (0.6)	2 (0.4)	5 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	3 (0.6)	4 (0.4)
Other	1 (0.2)	0	1 (0.1)
Multiple	2 (0.4)	4 (0.8)	6 (0.6)
Not reported	2 (0.4)	3 (0.6)	5 (0.5)
Unknown	0	0	0
Race group, n (%) [a]			
White	383 (77.1)	401 (79.9)	784 (78.5)
Black	92 (18.5)	85 (16.9)	177 (17.7)
Asian	13 (2.6)	4 (0.8)	17 (1.7)
Other	7 (1.4)	9 (1.8)	16 (1.6)
Missing	2 (0.4)	3 (0.6)	5 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	144 (29.0)	140 (27.9)	284 (28.4)
Not Hispanic or Latino	346 (69.6)	360 (71.7)	706 (70.7)
Not reported	5 (1.0)	0	5 (0.5)
Unknown	2 (0.4)	2 (0.4)	4 (0.4)
Height (cm)			
n	497	502	999
Mean (SD)	169.79 (10.528)	169.18 (9.687)	169.48 (10.113)
Median	168.90	169.25	169.00
Min, Max	139.7, 215.9	145.1, 203.0	139.7, 215.9
Weight (kg)			
n	497	502	999
Mean (SD)	95.43 (25.284)	95.44 (23.334)	95.44 (24.311)
Median	92.40	93.95	93.10
Min, Max	36.8, 222.3	38.6, 171.6	36.8, 222.3

	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
BMI (kg/m^2)			
n	497	502	999
Mean (SD)	32.99 (7.770)	33.32 (7.658)	33.16 (7.712)
Median	31.80	32.75	32.10
Min, Max	17.9, 66.4	16.2, 59.6	16.2, 66.4
BMI group, n (%)			
<30 kg/m^2	195 (39.2)	183 (36.5)	378 (37.8)
≥30 kg/m^2	302 (60.8)	319 (63.5)	621 (62.2)
BMI group, n (%)			
<40 kg/m^2	412 (82.9)	413 (82.3)	825 (82.6)
≥40 kg/m^2	85 (17.1)	89 (17.7)	174 (17.4)
Risk factor, n (%) [b]			
CAD/CHF	129 (26.0)	129 (25.7)	258 (25.8)
CAD	97 (19.5)	104 (20.7)	201 (20.1)
CHF	53 (10.7)	45 (9.0)	98 (9.8)
Chronic lung disease [c]	236 (47.5)	225 (44.8)	461 (46.1)
COPD	51 (10.3)	52 (10.4)	103 (10.3)
Asthma	193 (38.8)	195 (38.8)	388 (38.8)
Chronic respiratory disease	18 (3.6)	12 (2.4)	30 (3.0)
Pulmonary fibrosis	1 (0.2)	1 (0.2)	2 (0.2)
Type 1 or 2 DM	278 (55.9)	299 (59.6)	577 (57.8)
At least 2 risk factors [d]	150 (30.2)	149 (29.7)	299 (29.9)
At least 3 risk factors [d]	36 (7.2)	41 (8.2)	77 (7.7)
Risk group, n (%) [e]			
CAD/CHF	116 (23.3)	116 (23.1)	232 (23.2)
Chronic respiratory disease (COPD/asthma/PF)	162 (32.6)	157 (31.3)	319 (31.9)
Type I or II DM	219 (44.1)	229 (45.6)	448 (44.8)

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; eCRF = electronic case report form; IRT = interactive response technology; Max= maximum; Min = minimum; PF = pulmonary fibrosis; SD = standard deviation.

Percentages are based on the number of participants in the Safety Set.

Baseline value for height, weight and BMI is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected on or before the date of study injection.

BMI = (body weight in kilograms)/(height in meters)^2.

- Other race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple. Missing race includes Not Reported, Unknown, and Missing.
- Derived from data collected on Targeted Medical History eCRF. Participants may have more than one risk factor and counted more than once.
- Chronic lung disease includes COPD, asthma, pulmonary fibrosis, and other chronic respiratory disease.
- Derived from data collected on Targeted Medical History eCRF (including CAD, CHF, COPD, asthma, PF, and Type I or II DM).
- Risk group is based on IRT. Participants are counted for only one risk group.

Source: Table 14.1.3.4.1.

Study mRNA-1345-P301

In Study P301, the PPI Set included 1515 participants in the 50 µg group who received the assigned IP dose per-protocol, had RSV immunogenicity results at Baseline and at Day 29, and had no major protocol deviations. The random selection of the PPI Set was stratified by age (60 to 74 years and ≥75 years), by those with and without RSV-LRTD risk factors, and those from Northern and Southern hemispheres to ensure adequate representation for analysis of high-risk subgroups.

In the 50 µg group, the median (range) age was 72.0 (60 to 94) years with similar representation of Hispanic or Latino and not Hispanic and Latino ethnicity subgroup. The majority of participants were male (874/1515 [55.0%]) and White (1171/1515 [77.3%]).

At least one comorbidity of interest (including CHF, COPD, asthma, chronic respiratory disease, diabetes, advanced liver disease or advanced renal disease) was reported for 866/1515 (57.2%) participants. A BMI of 30 kg/m² or higher was reported in 473/1515 (31.2%) participants and the mean (SD) BMI was 27.62 (4.208) kg/m2 (range 18.0 to 35.1). An overview of the Baseline demographics and characteristics for the 50 µg group is presented in Module 2.7.3 Section 2.1.2, data not presented here.

Co-primary Immunogenicity Endpoints

The Study P303 co-primary immunogenicity objectives were to evaluate RSV-A and RSV-B nAb responses at Day 29 after a single 50 µg dose of mRNA-1345 compared to those observed in the pivotal P301 study which demonstrated clinical efficacy.

The co-primary immunogenicity endpoints were assessed by measuring nAb GMT at Day 29 (against RSV A and RSV-B) after a single dose of 50 µg mRNA-1345 in the Study P303 PP Set. These were compared to nAb GMT at Day 29 from the Study P301 PPI Set to determine the GMR.

The GMR (95% CI) at Day 29 was 1.163 (1.053, 1.285) and 1.135 (1.037, 1.242), for RSV-A and RSV-B, respectively (Table 2). Results met prespecified Study P303 NI criteria for the co-primary objectives and allow the effectiveness of a single dose of 50 µg mRNA-1345 to be inferred in adults ≥18 to ≤59 years at increased risk for RSV-LRTD.

Table 2: Day 29 nAb GMT and GMR (nAb against RSV-A and RSV-B) from Studies P303 (mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg; PPI Set)

	P303 N=494			P301 N=1515			P303 vs. P301	
nAb Titer (IU/mL)	N1	Model-Based GMT[a]	95% CI	N1	Model-Based GMT[a]	95% CI	GMR	95% CI
RSV-A	492	23245.01	(21326.32, 25336.34)	1513	19988.17	(19038.32, 20985.41)	1.163	(1.053, 1.285)
RSV-B	489	7830.71	(7242.04, 8467.23)	1511	6901.15	(6602.51, 7213.30)	1.135	(1.037, 1.242)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio, which is model-based; GMT = geometric mean titer; LLOQ = lower limit of quantification; LS = least square; nAb = neutralizing antibody; PP = per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; ULOQ = upper limit of quantification.

N1 = Number of participants with nonmissing antibody data at Baseline (Day 1) and Day 29.

Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ.

[a] The model-based GMT is estimated on ANCOVA model. In the ANCOVA model, the log-transformed antibody levels at Day 29 post baseline are treated as a dependent variable, with the treatment group as an explanatory variable and the log-transformed Baseline antibody level as a covariate. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation

Source: Study P303 CSR Table 14.2.1.1.1.1, Table 14.2.2.1.1.1.

Secondary Immunogenicity Endpoints

A secondary objective compared the SRR for Study P303 with that of Study P301. A seroresponse was defined as a 4-fold increase in antibody levels from Baseline (or from the assay LLOQ if Baseline levels were below the LLOQ). This secondary objective assessed the SRR difference at Day 29 (for RSV-A and RSV-B) following a single dose of 50 µg mRNA-1345 in Study P303 compared those in Study P301. The prespecified NI criterion defined success as a LB of the 95% CI for the SRR difference >-10%. These criteria were successfully met, providing further evidence of the effectiveness of the 50 µg dose in the P303 study population.

Immunogenicity analyses were conducted of induced immune responses by subgroups of age, sex, race, ethnicity and risk factor. Evaluation by age subgroups included comparison of nAb levels in Study P303 participants ≥18 to ≤49 years and those ≥50 to ≤59 years, to a younger age subset of Study P301 (60 to ≤69 years). Measures of RSV-specific bAb levels were also evaluated as secondary objectives in Study P303.

nAb Responses at Day 29

GMT and GMFR for Baseline and Day 29 nAb (RSV-A and RSV-B) nAb levels (GMT) and the GMFR measured from the 50 µg recipients in Studies P303 and P301 are summarized in Table 3.

Baseline titers in Study P303 were lower than those in Study P301; however, administration of 50 µg of mRNA-1345 led to comparable GMT point estimates at Day 29 (and overlapping 95% CI) for the 2 study populations. For RSV-A, GMT (95% CI) increased from 1560.76 IU/mL (1410.06, 1727.56) at Baseline to 19158.04 IU/mL (17336.35, 21171.16) at Day 29. For RSV-B, GMT (95% CI) increased from 1031.65 IU/mL (936.76, 1136.16) at Baseline to 6719.34 IU/mL (6108.93, 7390.73) at Day 29 (Table 3).

The comparable GMT values at Day 29 were the result of higher GMFR in the P303 study population

compared to the P301 study population. For RSV-A, the GMFR (95% CI) at Day 29 for Study P303 was 12.21 (11.09, 13.43), higher than that of Study P301 (8.33 [7.88, 8.80]). Similarly, for RSV-B the GMFR (95% CI) at Day 29 in Study P303 was 6.64 (6.08, 7.25), higher than that of Study P301 (5.10 [4.85, 5.35]) (Table 3).

Table 3: Summary of nAb GMT and GMFR (nAb Against RSV-A and RSV-B) from Studies P303 (mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg; PPI Set) by Visit

Timepoint Statistic	P303 N=494	P301 N=1515
RSV-A nAb Titer (IU/ml)		
Baseline (Day 1)		
n [a]	493	1514
GMT (95% CI[b])	1560.76 (1410.06, 1727.56)	2560.23 (2421.27, 2707.17)
Day 29		
n [a]	493	1514
GMT (95% CI[b])	19158.04 (17336.35, 21171.16)	21300.14 (20122.75, 22546.43)
N1	492	1513
GMFR (95% CI[b])	12.21 (11.09, 13.43)	8.33 (7.88, 8.80)
RSV-B nAb Titer (IU/mL)		
Baseline (Day 1)		
n [a]	493	1514
GMT (95% CI[b])	1031.65 (936.76, 1136.16)	1424.26 (1351.77, 1500.63)
Day 29		
n [a]	490	1512
GMT (95% CI[b])	6719.34 (6108.93, 7390.73)	7248.75 (6867.92, 7650.69)
N1	489	1511
GMFR (95% CI[b])	6.64 (6.08, 7.25)	5.10 (4.85, 5.35)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold-rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; GMFR = geometric mean fold rise; GMT = geometric mean titer; PP=per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; ULOQ = upper limit of quantification.

N1 = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint.

Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ.

a. Number of participants with non-missing data at the timepoint (Baseline or post-baseline).

b. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GMFR, respectively, then back transformed to the original scale for presentation.

Source: Study P303 CSR Table 14.2.1.2.1.1, Table 14.2.2.2.1.1.

SRR Difference Between Study P303 (PP Set) and P301 (PPI Set) for Day 29 nAb (RSV-A and RSV-B)

For Study P303, a seroresponse was defined at a participant level as a ≥4-fold rise from Baseline titer (when Baseline titer was ≥LLOQ) or a ≥4-fold rise from LLOQ (if Baseline was <LLOQ). The NI of the SRR for RSV-A and RSV-B nAb responses after administration of 50 µg mRNA-1345 in Study P303 compared to Study P301 was successfully demonstrated. The SRR and SRR difference values are presented in Table 4.

The SRR difference (95% CI) at Day 29 between the P303 and P301 study populations for RSV-A was 11.8% (7.8, 15.5) and for RSV-B was 10.8% (5.9, 15.6). Accordingly, the difference in SRR for both RSV-A and RSV-B met prespecified NI success criteria in adults ≥18 to ≤59 years at increased risk for RSV LRTD who received 50 µg of mRNA-1345.

Table 4: Day 29 nAb SRR and SRR difference (nAb against RSV-A and RSV-B) from Studies P303

(mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg; PPI Set)

	P303 N=494				P301 N=1515				P303 vs. P301	
nAb Titer (IU/mL)	n	N1	SRR (%)[a]	95% CI[b]	n	N1	SRR (%)[a]	95% CI[b]	SRR Difference (%)	95% CI[c]
RSV-A	422	492	85.8	(82.4, 88.7)	1119	1513	74.0	(71.7, 76.2)	11.8	(7.8, 15.5)
RSV-B	329	489	67.3	(62.9, 71.4)	853	1511	56.5	(53.9, 59.0)	10.8	(5.9, 15.6)

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantification; nAb = neutralizing antibody; PP = per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with nonmissing antibody data at Baseline (Day 1) and Day 29.

Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ.

a. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold increase if Baseline is equal to or above the LLOQ. Percentages are based on N1.

b. 95% CI is calculated using the Clopper-Pearson method.

c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: Study P303 CSR Table 14.2.1.1.1.1, Table 14.2.2.1.1.1.

SRR at Day 29 Based on nAb (RSV-A and RSV-B)

The proportion of participants in Studies P303 and P301 who met the standard definition of a seroresponse are summarized above. The Study P303 SRRs were higher than those in the older P301 population for both RSV-A and RSV-B (Table 4).

Since all Study P303 (and Study P301) participants had measurable nAb to RSV at Baseline (ie, Baseline nAb levels >the LLOQ), an alternative analysis was performed assessing the proportion of participants achieving a ≥2-fold increase in nAb level. This analysis permits assessment of vaccine activity in a population that has elevated antibody titers at Baseline and may face challenges in mounting a 4-fold increase from such elevated Baseline levels. The proportion of participants in Study P303 with a ≥2-fold increase from Baseline (95% CI) was 95.9% (93.8, 97.5) for RSV-A and 89.4% (86.3, 92.0) for RSV-B (Table 5), also higher than similar assessments in the Study P301 PPI Set.

Table 5: Summary of Day 29 nAb SRR (nAb against RSV-A and RSV-B) from Studies P303 (mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg; PPI Set)

Timepoint Statistic	P303 N=494	P301 N=1515
RSV-A nAb Titer (IU/mL)		
Seroresponse [a]		
n (%) [b]	422 (85.8)	1119 (74.0)
95% CI [c]	(82.4, 88.7)	(71.7, 76.2)
≥2-fold Increase from Baseline [d]		
n (%) [b]	472 (95.9)	1379 (91.1)
95% CI [c]	(93.8, 97.5)	(89.6, 92.5)
RSV-B nAb Titer (IU/mL)		
Seroresponse [a]		
n (%) [b]	329 (67.3)	853 (56.5)
95% CI [c]	(62.9, 71.4)	(53.9, 59.0)
≥2-fold Increase from Baseline [d]		
n (%) [b]	437 (89.4)	1271 (84.1)
95% CI [c]	(86.3, 92.0)	(82.2, 85.9)

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantification; nAb = neutralizing antibody; PP = per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint.

Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ.

a. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold increase if Baseline is equal to or above the LLOQ.

b. Number of participants meeting the criterion at the timepoint. Percentages are based on N1.

c. 95% CI is calculated using the Clopper-Pearson method.

d. ≥ z-fold increase from Baseline at participant level is defined as a change from below the LLOQ to equal or above z×LLOQ, or at least a z-fold increase if Baseline is equal to or above the LLOQ.

Source: Study P303 CSR Table 14.2.1.2.1.1, Table 14.2.2.2.1.1.

nAb Responses in Subgroups

The immunogenicity data at Day 29 were evaluated by prespecified subgroups based on age, sex, race, ethnicity, and risk factor. Risk factors in Study P303 are those associated at increased risk for RSV-LRTD and include CAD/CHF, chronic lung disease, and Type 1 or Type 2 DM. It is important to note that participants could have more than one risk factor. Indeed, 146/494 (29.6%) participants in the 50 µg PP Set had at least 2 risk factors and 39/494 (7.9%) had at least 3 risk factors.

In addition to the prespecified subgroup analyses, immune responses were also analyzed in subgroups of participants with a BMI >30 kg/m2 and those with a BMI >40 kg/m2, conditions increasingly recognized as placing adults at increased risk of RSV-LRTD. These results are also summarized below.

This section presents analyses of nAb by GMT, GMFR, and SRR, each by study subgroup. Responses are largely consistent across the subgroups in the Study P303 50 µg PP Set. This suggests that the effectiveness inferred for the Study P303 50 µg PP Set applies regardless of age, sex, race, ethnicity, risk factor, or BMI.

Subgroup analyses are presented for the 50 µg group. Results of individual subgroups are descriptive.

Age

Descriptive comparisons of nAb responses at Day 29 (RSV-A and RSV-B GMT, GMFR, SRR) were prespecified between age subgroups of 18 to 49 years (n=189) and 50 to 59 years (n=305) and those of the overall Study P303 50 µg PP Set.

Lower immunogenicity with older age was not observed in Study P301. Nevertheless, to provide the most conservative comparator for Study P303, comparison was also made between P303 age groups (18 to 59 years and 50 to 59 years) and a younger P301 age subset (60 to 69 years). Posthoc descriptive comparisons were performed for nAb GMT and SRR at Day 29 (for both RSV-A and RSV-B).

The summary of observed nAb responses (ie, GMT, GMFR, and SRR) is presented in Table 6. While Baseline GMT in Study P303 (both in the overall population and 50 to 59 years subgroup) were lower than those in the Study P301 60 to 69 years age subset, GMT at Day 29 for all P303 comparisons were consistent with those of the younger P301 subset, with overlapping 95% CIs. GMFRs for RSV-A and RSV-B in Study P303 (both overall and across age subgroups) were consistently higher than those in the Study P301 60 to 69 years subset.

Descriptive comparison of observed nAb levels at Day 29 were made between Study P303 overall PP Set and the 2 age subgroups (18 to 49 years; 50 to 59 years). GMT and SRR at Day 29 (for RSV-A and RSV B) by age subgroups were largely consistent with results of the overall PP Set (Table 6).

Calculation of the GMR (ANCOVA model-based GMT at Day 29) for each P303 to P301 age group comparison further illustrated this comparability. For the P303 50- to 59-year subgroup vs. the P301 60- to 69-year subset, the GMR for RSV-A was 1.017 (95% CI: 0.892, 1.159) and for RSV-B was 1.036 (95% CI: 0.919, 1.169). For the overall P303 18- to 59-year group vs. the P301 60- to 69-year subset, the GMR for RSV-A was 1.043 (95% CI: 0.932, 1.169) and for RSV-B was 1.065 (95% CI: 0.959, 1.183).

Table 6: Summary of nAb GMT, GMFR, and SRR (nAb Against RSV-A and RSV-B nAb) by Visit and Age Group from Studies P303 (mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg PPI Set)

Test Parameter Timepoint Data Category Statistics	P303 Overall N=494	P303 18 to 49 years N=189	P303 50 to 59 years N=305	P301 60 to 69 years N=619
RSV-A nAb Titer (IU/mL)				
Baseline, n [a]	493	189	304	619
GMT (95% CI) [b]	1560.76 (1410.06, 1727.56)	1431.75 (1227.14, 1670.47)	1646.76 (1439.96, 1883.26)	2308.86 (2123.34, 2510.60)
Day 29, n [a]	493	189	304	619
GMT (95% CI) [b]	19158.04 (17336.35, 21171.16)	18977.25 (16201.75, 22228.21)	19271.31 (16930.42, 21935.87)	22516.65 (20659.30, 24540.99)
N1	492	189	303	619
GMFR (95% CI) [b]	12.21 (11.09, 13.43)	13.25 (11.38, 15.43)	11.59 (10.25, 13.12)	9.75 (8.97, 10.61)
SRR [c], n (%) [d]	422 (85.8)	163 (86.2)	259 (85.5)	493 (79.6)
(95% CI) [e]	(82.4, 88.7)	(80.5, 90.8)	(81.0, 89.2)	(76.3, 82.7)
≥2-fold increase from Baseline [f], n (%) [d]	472 (95.9)	182 (96.3)	290 (95.7)	583 (94.2)
(95% CI) [e]	(93.8, 97.5)	(92.5, 98.5)	(92.8, 97.7)	(92.0, 95.9)
RSV-B nAb Titer (IU/mL)				
Baseline, n [a]	493	188	305	618
GMT (95% CI) [b]	1031.65 (936.76, 1136.16)	938.94 (803.06, 1097.81)	1093.30 (966.88, 1236.26)	1349.08 (1244.01, 1463.03)
Day 29, n [a]	490	188	302	617
GMT (95% CI) [b]	6719.34 (6108.93, 7390.73)	6678.02 (5702.91, 7819.85)	6745.19 (5982.60, 7604.98)	7456.56 (6857.30, 8108.20)
N1	489	187	302	616
GMFR (95% CI) [b]	6.64 (6.08, 7.25)	7.20 (6.21, 8.34)	6.31 (5.66, 7.04)	5.54 (5.14, 5.98)
SRR [c], n (%) [d]	329 (67.3)	128 (68.4)	201 (66.6)	357 (58.0)
(95% CI) [e]	(62.9, 71.4)	(61.3, 75.0)	(60.9, 71.9)	(53.9, 61.9)
≥2-fold increase from Baseline [f], n [d]	437 (89.4)	166 (88.8)	271 (89.7)	535 (86.9)
(95% CI) [e]	(86.3, 92.0)	(83.3, 92.9)	(85.7, 92.9)	(83.9, 89.4)

Abbreviations: CI = confidence interval; eCRF = electronic case report form; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; nAb = neutralizing antibody; PP = per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with non-missing data at Baseline and Day 29.

Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ.

Risk Factor is derived from data collected on Targeted Medical History eCRF.

- Number of participants with non-missing data at the timepoint (Baseline or post-baseline).
- 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold rise, respectively, then back transformed to the original scale for presentation.
- Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold increase if Baseline is equal to or above the LLOQ.
- Number of participants meeting the criterion at the timepoint. Percentages are based on N1.
- 95% CI is calculated using the Clopper-Pearson method.
- ≥z-fold increase from Baseline at participant level is defined as a change from below the LLOQ to equal or above z×LLOQ, or at least a z-fold increase if Baseline is equal to or above the LLOQ.

Source: Study P303 CSR Table 14.2.1.2.1.1, Table 14.2.2.2.1.1, Table 14.2.1.2.2.1.4, Table 14.2.2.2.2.1.4; Table 14.2.3.1.2.3, Table 14.2.3.2.2.3.

Sex

nAb responses were assessed by subgroups of sex: females (n=265) and males (n=229). Across all analyses of nAb responses, results in men and women were consistent with those of the Study P303 50 µg PP Set.

Race

nAb responses were evaluated according to subgroups of race, including White (n=396), Black (n=83), Asian (n=4), and other (n=9) (information on race was absent for 2 participants) for Study P303 (refer to Module 2.7.3 Section 2.2.2.2.3, data not shown here). The nAb responses in subgroups with significant representation (ie, White, Black, and other) were consistent with those observed in the Study P303 50 µg PP Set. Meaningful conclusions are limited however, for subgroups with smaller numbers (ie, Asian, Other, and Missing).

Ethnicity

The ethnicity subgroups included Hispanic or Latino (n=136) and not Hispanic or Latino (n=356). The

nAb responses were largely consistent with those observed in the Study P303 50 µg PP Set across all analyses.

RSV-LRTD Risk Factor

The Study P303 subgroups for RSV-LRTD risk factors included CAD/CHF (n=127), chronic lung disease (n=218), and Type 1 or 2 DM (n=295) (Table 7). nAb responses were consistent with those of the 50 µg PP Set for all subgroups. This consistency was evident regardless of participants potentially reporting more than one risk factor.

Table 7: Summary of nAb GMT, GMFR, and SRR (nAb Against RSV-A and RSV-B) by Visit and Risk Factor Subgroup (Study P303, mRNA-1345 50 µg; PP Set)

Test Parameter Timepoint	CAD/CHF		Chronic Lung Disease (COPD/Asthma/Other CRD/PF)		Type 1 or 2 DM	
Data Category Statistics	Absent N=367	Present N=127	Absent N=276	Present N=218	Absent N=199	Present N=295
RSV-A nAb Titer (IU/mL)						
Baseline, n [a]	366	127	275	218	199	294
GMT (95% CI) [b]	1522.10 (1356.56, 1707.84)	1677.75 (1353.12, 2080.25)	1587.76 (1380.55, 1826.06)	1527.35 (1316.99, 1771.32)	1532.11 (1304.08, 1800.02)	1580.45 (1385.71, 1802.56)
D29, n [a]	366	127	275	218	199	294
GMT (95% CI) [b]	18828.53 (16754.87, 21158.84)	20140.28 (16560.38, 24494.05)	19254.97 (16816.97, 22046.42)	19036.46 (16398.65, 22098.59)	18106.10 (15640.05, 20960.99)	19904.54 (17380.24, 22795.48)
N1	365	127	274	218	199	293
GMFR (95% CI) [b]	12.28 (11.00, 13.70)	12.00 (9.83, 14.65)	12.00 (10.55, 13.66)	12.46 (10.79, 14.40)	11.82 (10.22, 13.67)	12.48 (10.98, 14.18)
SRR [c], n (%) [d]	315 (86.3)	107 (84.3)	237 (86.5)	185 (84.9)	171 (85.9)	251 (85.7)
(95% CI) [e]	(82.3, 89.7)	(76.7, 90.1)	(81.9, 90.3)	(79.4, 89.3)	(80.3, 90.4)	(81.1, 89.5)
≥2-fold Increase from Baseline [f], n (%) [d]	354 (97.0)	118 (92.9)	259 (94.5)	213 (97.7)	192 (96.5)	280 (95.6)
(95% CI) [e]	(94.7, 98.5)	(87.0, 96.7)	(91.1, 96.9)	(94.7, 99.3)	(92.9, 98.6)	(92.5, 97.6)
RSV-B nAb Titer (IU/mL)						
Baseline, n [a]	366	127	276	217	198	295
GMT (95% CI) [b]	1018.16 (912.62, 1135.91)	1071.55 (873.26, 1314.87)	961.17 (844.84, 1093.53)	1128.81 (975.82, 1305.80)	1130.33 (966.39, 1322.08)	970.30 (858.43, 1096.75)
D29, n [a]	366	124	273	217	197	293
GMT (95% CI) [b]	6855.55 (6131.35, 7665.28)	6332.88 (5268.55, 7612.23)	6162.98 (5448.24, 6971.50)	7491.15 (6455.28, 8693.25)	6880.71 (5953.63, 7952.16)	6612.97 (5825.73, 7506.59)
N1	365	124	273	216	196	293
GMFR (95% CI) [b]	6.73 (6.07, 7.46)	6.37 (5.36, 7.57)	6.59 (5.85, 7.41)	6.70 (5.86, 7.66)	6.30 (5.49, 7.23)	6.87 (6.13, 7.71)
SRR [c], n (%) [d]	239 (65.5)	90 (72.6)	183 (67.0)	146 (67.6)	133 (67.9)	196 (66.9)
(95% CI) [e]	(60.4, 70.4)	(63.8, 80.2)	(61.1, 72.6)	(60.9, 73.8)	(60.8, 74.3)	(61.2, 72.3)
≥2-fold Increase from Baseline [f], n (%) [d]	329 (90.1)	108 (87.1)	242 (88.6)	195 (90.3)	173 (88.3)	264 (90.1)

Test Parameter Timepoint	CAD/CHF		Chronic Lung Disease (COPD/Asthma/Other CRD/PF)		Type 1 or 2 DM	
Data Category Statistics	Absent N=367	Present N=127	Absent N=276	Present N=218	Absent N=199	Present N=295
(95% CI) [e]	(86.6, 93.0)	(79.9, 92.4)	(84.3, 92.2)	(85.5, 93.9)	(82.9, 92.4)	(86.1, 93.3)

Abbreviations: CI = confidence interval; CAD = coronary artery disease; CHF = congestive heart failure; CLD = chronic lung disease; COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; DM = diabetes mellitus; eCRF = electronic case report form; PP = per-protocol; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; Max = maximum; Min = minimum; nAb = neutralizing antibody; PF = pulmonary fibrosis; PP = per-protocol; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with non-missing data at Baseline and Day 29.

Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5×LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ.

Risk Factor is derived from data collected on Targeted Medical History eCRF.

a. Number of participants with non-missing data at the timepoint (Baseline or post-baseline).

b. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GMFR, respectively, then back transformed to the original scale for presentation.

c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold increase if Baseline is equal to or above the LLOQ.

d. Number of participants meeting the criterion at the timepoint. Percentages are based on N1.

e. 95% CI is calculated using the Clopper-Pearson method.

f. ≥z-fold increase from Baseline at participant level is defined as a change from below the LLOQ to equal or above z×LLOQ, or at least a z-fold increase if Baseline is equal to or above the LLOQ.

Source: Study P303 CSR Table 14.2.1.2.2.1.1, Table 14.2.2.2.2.1.1, Table 14.2.1.2.2.1.2, Table 14.2.2.2.2.1.2, Table 14.2.1.2.2.1.3, Table 14.2.2.2.2.1.3.

Body Mass Index

Study P303 BMI subgroups included participants with BMI <30 (n=180), BMI ≥30 (n=314), BMI <40 (n=406), and BMI ≥40 (n=88) (refer to Module 2.7.3 Section 2.2.2.2.6, data not shown here). nAb responses were consistent with those observed in the 50 µg PP Set for all BMI subgroups. Results suggests that individuals at increased risk of RSV-LRTD by virtue of increased BMI nonetheless show consistent nAb responses following a single dose of 50 µg of mRNA-1345 as the 50 µg PP Set.

nAb Responses at Day 181

This section summarizes nAb responses (GMT, GMFR, and SRR) at Day 181 post-injection to provide data regarding the durability of induced responses. Additionally, descriptive comparison of nAb responses at Day 181 in the 50 µg P303 PP Set are made to those from Day 181 Study P301 PPI Set.

Immunogenicity at Day 181 was evaluated in 494 participants from the 50 µg mRNA-1345 group in Study P303 PP Set and 1515 participants from Study P301 PPI Set. GMT, GMFR, and SRR, as measured by nAbs, were analyzed as a secondary immunogenicity endpoint.

GMR and SRR Difference Between Study P303 (PP Set) and Study P301 (PPI Set) for Day 181 nAb (RSV-A and RSV-B)

The GMR (95% CI) at Day 181 between Studies P303 and P301 was 1.143 (1.034, 1.262) for RSV-A, and 1.153 (1.057, 1.258) for RSV-B (Table 8). The LB of the 95% CI was >0.667 for both RSV subtypes. Similarly, SRR difference (95% CI) at Day 181 between Studies P303 and P301 study populations for RSV-A was 13.8% (8.7, 19.0) and for RSV-B was 11.4% (6.8, 16.3) (Table 8). The LB of the 95% CI was >-10% for both RSV subtypes. Although not prespecified, this analysis would have met the NI criteria had it been a formal objective even 6 months after a single dose of 50 µg mRNA-1345.

Table 8: Day 181 nAb GMT, GMR, SRR, and SRR Difference (nAb Against RSV-A and RSV-B) from Studies P303 (mRNA-1345 50 µg; PP Set) and P301 (mRNA-1345 50 µg; PPI Set)

	P303 50 µg N=494	P301 50 µg N=1515
RSV-A nAb Titer (IU/mL)		
N1	464	1401
Model-Based Day 181 GMT [a] (95% CI)	7554.24 (6931.13, 8233.37)	6611.65 (6295.22, 6943.98)
GMR (95% CI)	1.143 (1.034, 1.262)	
SRR n (%) [b]	216 (46.6)	459 (32.8)
95% CI [c]	(41.9, 51.2)	(30.3, 35.3)
SRR Difference (%) 95% CI [d]	13.8 (8.7, 19.0)	
RSV-B nAb Titer (IU/mL)		
N1	455	1401
Model-Based Day 181 GMT [a] (95% CI)	3071.44 (2847.46, 3313.03)	2663.61 (2551.67, 2780.48)
GMR (95% CI)	1.153 (1.057, 1.258)	

	P303 50 µg N=494	P301 50 µg N=1515
SRR n (%) [b]	142 (31.2)	277 (19.8)
95% CI [c]	(27.0, 35.7)	(17.7, 22.0)
SRR Difference (%) 95% CI [d]	11.4 (6.8, 16.3)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio (model-based); GMT = geometric mean titer; LLOQ = lower limit of quantification; PP = per-protocol; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with nonmissing antibody data at Baseline (Day 1) and D29.

Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5×LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ.

[a] The model-based GMT is estimated on Analysis of covariance (ANCOVA) model. In the ANCOVA model, the log-transformed antibody levels at Day 29 post baseline are treated as a dependent variable, with the treatment group as an explanatory variable and the log-transformed Baseline antibody level as a covariate. The resulted least square (LS) means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold increase if Baseline is equal to or above the LLOQ. Percentages are based on N1.

[c] 95% CI is calculated using the Clopper-Pearson method.

[d] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: Study P303 CSR Table 14.2.1.1.1.3, Table 14.2.2.1.1.3.

GMT, GMFR, and SRR for Baseline and Day 181 nAb (RSV-A and RSV-B)

For RSV-A in Study P303, GMT (95% CI) increased from 1560.76 IU/mL (1410.06, 1727.56) at Baseline to 6031.83 IU/mL (5442.57, 6684.88) at Day 181. For RSV-B, GMT (95% CI) increased from 1031.65 IU/mL (936.76, 1136.16) at Baseline to 2628.66 IU/mL (2382.98, 2899.66) at Day 181 (refer to Module 2.7.3 Section 2.2.2.3.2, data not shown here).

While Baseline titers in Study P303 were lower than those observed in Study P301 for both RSV-A and RSV-B, the administration of 50 µg mRNA-1345 resulted in GMT at Day 181 that were similar for RSV-B across studies, with overlapping 95% CIs. For RSV-A, however, the GMT at Day 181 was lower in the P303 group. Despite these differences, the GMFR by Day 181 was higher in Study P303 compared to Study P301. Specifically, the GMFR (95% CI) at Day 181 for RSV-A in Study P303 was 3.98 (3.62, 4.37), compared to 2.81 (2.66, 2.97) in Study P301. Similarly, for RSV-B, the GMFR (95% CI) at Day 181 in Study P303 was 2.62 (2.40, 2.87), compared to 1.99 (1.89, 2.08) in Study P301.

The proportion of participants with nAbs titers ≥4-fold higher than Baseline (95% CI) at Day 181 was 46.6% (41.9, 51.2) for RSV-A and 31.2% (27.0, 35.7) for RSV-B. The proportion of participants with ≥2-fold increases from Baseline (95% CI) was 72.6% (68.3, 76.6) for RSVA and 58.2% (53.6, 62.8) for RSV-B.

<u>bAb Responses at Day 29</u>

While the primary endpoints of Study P303 were based on nAb, analyses of bAb responses were performed as secondary endpoints. This section summarizes bAb responses at Day 29 against the preF conformation of the RSV F protein. Results show that nAb and bAb responses show similar trends across both studies, further supporting the inference of effectiveness in adults ≥18 to ≤59 years at increased risk for RSV-LRTD.

GMR (and GMC) of Study P303 (PP Set) Compared to Study P301 (PPI Set) for Day 29 RSV PreF bAb

The bAb responses (preF) at Day 29 in the Study P303 50 µg group were compared to those observed

in Study P301. The bAb GMR (95% CI) was 1.178 (1.096, 1.267), consistent with the GMR between the 2 studies for the nAb responses. While measure of bAb responses was not a prespecified NI analysis, the consistent pattern of GMR for nAb and bAb further supports the inference of effectiveness in adults ≥18 to ≤59 years at increased risk for RSV-LRTD.

GMC and GMFR for Baseline and Day 29 RSV PreF bAbs

Results of RSV preF bAb levels (GMC) and the fold-rise from Baseline (GMFR) measured from recipients of mRNA-1345 50 µg in Studies P303 and P301 are summarized in Module 2.7.3 Section 2.2.2.4.2, data not shown here.

Although Baseline GMC in Study P303 was lower than that in Study P301, administration of 50 µg of mRNA-1345 resulted in a higher GMC at Day 29 in the P303 study population. This was due to the higher GMFR (95% CI) observed in the P303 study population compared to the P301 study population: 9.78 (9.07, 10.54) in Study P303 compared to 7.63 (7.32, 7.97) in Study P301.

In Study P303, GMC (95% CI) increased from 9313.95 AU/mL (8735.16, 9931.09) at Baseline to 91171.85 AU/mL (85584.94, 97123.46) at Day 29.

SRR Difference Between Study P303 (50 µg, PP Set) and Study P301 (PPI Set) for Day 29 PreF bAb

The bAb SRR difference (95% CI) between Studies P303 and P301 50 µg groups was 7.2% (3.3, 10.7), reinforcing the comparability of the 50 µg dose in younger adults at increased risk for RSV-LRTD.

SRR at Day 29 Based on PreF bAb

All participants had measurable RSV preF bAb levels at Baseline.

The proportion of Study P303 participants (50 µg group) meeting the standard definition of seroresponse (SRR, 95% CI) was 86.2% (82.8, 89.1) and 97.4% (95.5, 98.6), respectively.

Reflecting that all P303 study participants had measurable bAb levels at baseline, an analysis was also performed to measure the proportion of participants meeting a ≥2-fold increase from Baseline: a total of 97.4% (95.5, 98.6) participants met this definition

The SRR in the younger Study P303 study population were higher than those in the Study P301 population for RSV preF bAb.

bAb Responses in Subgroups

bAb responses across the prespecified subgroups of age, sex, race, ethnicity, RSV-LRTD risk factor, and BMI were largely consistent with the results of the Study P303 50 µg group. This suggests that the effectiveness inferred for the Study P303 50 µg group is expected to apply regardless of individual subgroup.

Immunogenicity Summary and Conclusion

The effectiveness of the mRNA-1345 50 µg dose for the prevention of RSV-LRTD in adults ≥18 to ≤59 years at increased risk for RSV-LRTD was demonstrated by immunobridging to the older adult population in Study P301. Key findings supporting this conclusion are summarized below:

- The primary immunogenicity objective was met by demonstrating NI of the GMR (95% CI) of nAbs against both RSV-A (1.163 [1.053, 1.285]) and RSV-B (1.135 [1.037, 1.242]) after a 50 µg dose compared to adults ≥60 years from Study P301.
- A secondary objective, based on SRR differences for nAbs against RSV-A and RSVB, also met predefined NI criteria when compared to Study P301. The SRR difference for the 50 µg group was 11.8% (95% CI: 7.8, 15.5) for RSV-A and 10.8% (95% CI: 5.9, 15.6) for RSV-B, further

supporting the effectiveness of the 50 µg dose in this younger, at-risk population.

- Immunogenicity responses, including GMT, SRR, and GMFR from Baseline to Day 29, were consistent across subgroups defined by age, sex, race, ethnicity, risk factors, and BMI.
- The immunogenicity responses in adults ≥18 to ≤59 years (and the subgroup of 50 to 59 years) at increased risk for RSV-LRTD were comparable to those of adults 60 to 69 years in the pivotal P301 study, supporting immunobridging to an age group closer to that of the P303 target population.
- The bAb responses followed a similar pattern to those of nAb responses, reinforcing the consistency of the immune response to mRNA-1345.
- Durability of the immune response was demonstrated, with elevated nAb titers sustained through 6 months post-vaccination, consistent with the durability observed in Study P301.

The MAH claims that these findings confirm that the 50 µg dose elicits effective and durable immune responses, which are likely to translate to prevention of RSV-LRTD, supporting its use in younger adults at increased risk for RSV-LRTD.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9. Summary of Efficacy for trial mRNA-1345-P303

Title: A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults – Part A		
Study identifier	mRNA-1345-P303	
Design	randomized, observer-blind pivotal safety and immunogenicity study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	18-59 yoa with increased risk of RSV-LRTD	50 µg mRNA-1345. n=502
	60 yoa and older comparator group pivotal study P301	50 µg mRNA-1345. n≈1,500

Endpoints and definitions	Primary endpoint	Immunogenicity	To evaluate the immune response to RSV-A and RSV-B nAbs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3 efficacy trial (mRNA-1345-P301).		
	Secondary endpoint	SRR	Non-inferiority of SRR after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3 efficacy trial (mRNA-1345-P301).		
Data cut-off date	18 September 2024				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Per protocol / DCO 18 Sep 2024				
Descriptive statistics and estimate variability	Treatment group	Study P303	Study P301	n/a	
	Number of subject	N=492 / 489	N=1513 / 1511	n/a	
	GMT (RSV-A)	23245.01	19988.17	n/a	
	95% CI	21326.32, 25336.34	19038.32, 20985.41	n/a	
	GMT (RSV-B)	7830.71	6901.15	n/a	
	95% CI	7242.04, 8467.23	6602.51, 7213.30	n/a	
Effect estimate per comparison	GMR (RSV-A)	1.163		n/a	
	95% CI	1.053, 1.285		n/a	
	GMR (RSV-B)	1.135		n/a	
	95% CI	1.037, 1.242		n/a	
Notes	ANCOVA model based GMT and GMR values.				

Analysis description	Secondary analysis
SRR difference RSV-A	11.8
95% CI	7.8, 15.5
SRR difference RSV-B	10.8
95% CI	5.9, 15.6

2.4.2. Discussion on clinical efficacy

Study mRNA-1345-P303 (P303) Part A was conducted to infer effectiveness of mRNA-1345 in adults ≥18 to ≤59 years of age considered at increased risk for RSV-LRTD. The rationale for development of mRNA-1345 for the adult population with comorbidities with increased risk for RSV-LRTD is well documented and acknowledged. The change to the indication in SmPC section 4.1 reflects this population appropriately.

Immunobridging by demonstration of non-inferiority in terms of the ratio of GM titres (GMR) in the age group ≥18 to 59 yoa from Study P303 as compared to the age group ≥60 yoa from Study P301 is acceptable to the CHMP. Non-inferiority criteria for the immunogenicity co-primary endpoints, ie non-inferiority of GMR against RSV-A and RSV-B, respectively, with the lower bound of the CI (95%) ≥0.667 are commonly used and endorsed by the CHMP.

Study P303 Part A included two doses for mRNA-1345 vaccination with 30 µg dose and 50 µg dose. Only results from study P303 Part A 50 µg mRNA-1345 were discussed which is acceptable to the CHMP. The 50 µg dose is approved in adults ≥60 yoa based on results from pivotal Study P301, and is the dose for the requested extension of the indication.

In study P303 (50µg dose cohort) only 5.2% of the subjects were 18 to 29 yoa, and 9.4% of the subjects were 30 to 39 yoa. The age group 50 to 59 yoa with a portion of 61.0% represented the majority of participants. Co-morbidities that increase the risk for RSV-LRTD, despite from DM type I, are expected to be fewer in younger adults which is most likely reflected in the demographics.

The co-primary immunogenicity endpoints were assessed by measuring nAb GMT at Day 29 (against RSV A and RSV-B) after a single dose of 50 µg mRNA-1345 in the Study P303. These were compared to nAb GMT at Day 29 from the Study P301 to determine the GMR. Results met Study P303 non-inferiority criteria for the immunogenicity co-primary endpoints. These results were obtained with ANCOVA model-based GMT values. Non-ANCOVA model-based GMT values from 50 µg dose recipients in P303 are slightly lower than 50 µg dose recipients in P301, however, baseline titres in P301 participants are substantially higher (1.64-fold and 1.38-fold for RSV-A and RSV-B, respectively) than in P303 participants.

There is no explanation in the documentation initially provided by the MAH on whether samples from studies P301 and P303 have been analysed concurrently or results from study P301 were used from the previous immunogenicity analysis. Justification from the MAH was requested by the CHMP on how these values can be considered comparable. The MAH clarified that internal quality samples were used during immunogenicity testing which is considered acceptable to the CHMP.

Non-inferiority in terms of GMR and SRR could also have been demonstrated 6 months after study vaccination, although it was not a formal endpoint for this analysis.

An analysis of bAb against preF demonstrated a GMFR (95% CI) of 9.78 (9.07, 10.54) in P303 participants compared to 7.63 (7.32, 7.97) in study P301 participants, and SRR difference (95% CI) between Studies P303 and P301 50 µg groups of 7.2% (3.3, 10.7), which mirrors results from nAb analyses.

The secondary endpoint of SRR difference at Day 29 between the P303 and P301 study populations for RSV-A was 11.8% (7.8, 15.5) and for RSV-B was 10.8% (5.9, 15.6). Accordingly, the difference in SRR for both RSV-A and RSV-B met non-inferiority success criteria in adults ≥18 to ≤59 years at increased risk for RSV LRTD who received 50 µg of mRNA-1345.

Sub-group analyses did not demonstrate differences in nAb responses 29 days after receipt of 50 µg mRNA-1345 influenced by age, sex, race, ethnicity, LRTD risk factor, or BMI. The CHMP noted that numbers of participants in particular sub-group analyses, e.g. for race sub-groups, were too small to allow a meaningful interpretation.

2.4.3. Conclusions on the clinical efficacy

The rationale for development of mRNA-1345 for the adult population with comorbidities with increased risk for RSV-LRTD is well documented and acknowledged by the CHMP. The change to the indication in SmPC section 4.1 reflects this population appropriately.

Non-inferiority criteria for the immunogenicity co-primary endpoints are commonly used and acceptable to the CHMP.

The CHMP is of the opinion that results met study P303 non-inferiority criteria for the immunogenicity co-primary endpoints, as well as secondary endpoints.

2.5. Clinical safety

The submission reviews safety data from a total of 999 participants in the Study P303 Safety Set. Of the 1003 participants randomized, 4 did not receive any dose of mRNA 1345. The Safety Set therefore comprises the 999 participants who received a dose of mRNA-1345, including 502 participants who received the 50 µg dose. The median duration of study follow-up was 253 days (Safety Set; range: 8 to 349 days).

As of the DCO (18 Sep 2024), a total of 29 participants from the Safety Set had discontinued the study. A total of 980 participants (999 in the Safety Set less the 19 participants who discontinued prior to reaching Day 180) completed at least 6 months of follow-up.

This section summarizes tolerability for the 50 µg group (n=502) and safety for the total study population (n = 999; participants receiving 30 or 50 µg of mRNA-1345). As such, all unsolicited safety findings are summarized. Results from Study P303 are viewed in the context of the pivotal P301 Study with n=18,231 exposed participants ≥60 years (mRESVIA Product Information).

The following safety data from Study P303 are presented in this section:

- Solicited local and systemic ARs: Collected via eDiary for 7 days post-injection.
- Unsolicited AEs: All AEs are collected for 28 days post injection.
- Deaths, SAEs, AEs leading to discontinuation from study, and AESIs are collected up to EOS. MAAEs are collected to Day 181.

In Study P303, AESIs were defined in the protocol as unsolicited AEs that were considered by the Investigator to represent protocol-defined medical concepts including thrombocytopenia, new onset or worsening of prespecified neurologic diseases (Bell's palsy/facial paralysis, GBS, ADEM, and seizures), anaphylaxis, and myocarditis/pericarditis. The protocol-defined AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines (Brighton Collaboration 2019).

Any suspected case of myocarditis, pericarditis, or myo-pericarditis was reviewed by the CEAC to determine if they met CDC criteria of "probable" or "confirmed" events (Gargano et al 2021; CDC Working Case Definitions are provided in the Study P303 Protocol. Further analysis of AEs of clinical interest was performed using programmed SMQs. The SMQs were selected to facilitate assessment of potential risks of mRNA-1345 use and/or were based on risks observed with other vaccines.

Unsolicited AEs were summarized based on the Safety Set. Unsolicited AEs, SAEs, MAAEs, AESIs, and AEs leading to discontinuation were summarized by SOC and PT or by PT only. AEs were coded by level of hierarchy (e.g., SOC, HLGT, PT) using MedDRA Version 25.0.

Study Participant Population

Of 501 participants randomized to the 50 µg group in Study P303 (Randomized Set), 14 (2.8%) participants discontinued the study. From the day of study injection (Day 1), the median duration of follow-up was 253 days (range: 8 to 349 days) in the 50 µg group. At the DCO date 492/502 (98.0%) participants in the 50 µg group had completed at least 180 days of post-injection follow-up.

Of the 1003 participants randomized in the total study population (Randomized Set), 33 (3.3%) participants discontinued the study including 4 who did not receive any dose of mRNA-1345. From the day of study injection (Day 1), the median duration of follow-up was 253 days (range: 8 to 349 days) in the total study population. The DCO date was triggered by the time at which all ongoing study participants had completed at least 180 days of post-injection follow-up; 980/999 (98.1%) participants in the total study population reached ≥6 months of post-injection follow-up at DCO.

Solicited Adverse Reactions

Overall Summary of Solicited Adverse Reactions

Compared with the older P301 population, the incidence of solicited local ARs was higher in the younger P303 population. The incidence of solicited systemic ARs was comparable between the 2 populations.

The finding that the incidence of solicited local ARs was higher in the younger P303 population; the CHMP requested its inclusion in the section 4.8 of the SmPC.

Regardless, most solicited local and systemic ARs in P303 were Grade 1 or 2 in severity, had an onset within 1 to 2 days post injection, and had a median duration of 2 days.

Table 10: Summary of Participants with Solicited Adverse Reactions Within 7 Day After Injection by Toxicity Grade from Studies P303 and P301 (mRNA-134 50 µg; Solicited Safety Sets)

Solicited Adverse Reaction Category Grade	P303 (N=502)	P301 (N=18,174)
Solicited Adverse Reactions - N1	502	18,174
Any Solicited Adverse Reactions	397 (79.1)	12,383 (68.1)
95% CI	75.3, 82.6	67.5, 68.8
Grade 1	200 (39.8)	8491 (46.7)
Grade 2	161 (32.1)	2777 (15.3)
Grade 3	35 (7.0)	1080 (5.9)
Grade 4	1 (0.2)	35 (0.2)
Grade 3 or Grade 4	36 (7.2)	1115 (6.1)
Solicited Local Adverse Reactions - N1	502	18,171
Any Solicited Local Adverse Reactions	374 (74.5)	10,591 (58.3)
95% CI	70.5, 78.3	57.6, 59.0
Grade 1	254 (50.6)	9251 (50.9)
Grade 2	110 (21.9)	779 (4.3)
Grade 3	9 (1.8)	561 (3.1)
Grade 3 or Grade 4	10 (2.0)	561 (3.1)
Pain - N1	502	18,170
Any	371 (73.9)	10,161 (55.9)
Grade 1	262 (52.2)	9268 (51.0)
Grade 2	101 (20.1)	585 (3.2)
Grade 3	7 (1.4)	308 (1.7)
Grade 3 or Grade 4	8 (1.6)	308 (1.7)
Erythema (Redness) - N1	502	18,168
Any	12 (2.4)	364 (2.0)
Grade 1	7 (1.4)	186 (1.0)
Grade 2	5 (1.0)	72 (0.4)
Grade 3	0	106 (0.6)
Grade 3 or Grade 4	0	106 (0.6)

Swelling (Hardness) - N1	502	18,169
Any	23 (4.6)	673 (3.7)
Grade 1	13 (2.6)	374 (2.1)
Grade 2	9 (1.8)	143 (0.8)
Grade 3	1 (0.2)	156 (0.9)
Grade 3 or Grade 4	1 (0.2)	156 (0.9)
Axillary (Underarm) Swelling or Tenderness - N1	502	18,168
Any	86 (17.1)	2764 (15.2)
Grade 1	71 (14.1)	2404 (13.2)
Grade 2	12 (2.4)	222 (1.2)
Grade 3	3 (0.6)	138 (0.8)
Grade 3 or Grade 4	3 (0.6)	138 (0.8)
Solicited Systemic Adverse Reactions - N1	502	18,171

Solicited Adverse Reaction Category Grade	P303 (N=502)	P301 (N=18,174)
Any Solicited Systemic Adverse Reactions	261 (52.0)	8613 (47.4)
95% CI	47.5, 56.4	46.7, 48.1
Grade 1	113 (22.5)	5259 (28.9)
Grade 2	119 (23.7)	2635 (14.5)
Grade 3	29 (5.8)	684 (3.8)
Grade 4	0 (0.0)	35 (0.2)
Grade 3 or Grade 4	29 (5.8)	719 (4.0)
Fever - N1	502	18,160
Any	18 (3.6)	502 (2.8)
Grade 1	9 (1.8)	269 (1.5)
Grade 2	6 (1.2)	122 (0.7)
Grade 3	3 (0.6)	76 (0.4)
Grade 4	0 (0.0)	35 (0.2)
Grade 3 or Grade 4	3 (0.6)	111 (0.6)
Headache - N1	502	18,167
Any	167 (33.3)	4856 (26.7)
Grade 1	86 (17.1)	3776 (20.8)
Grade 2	73 (14.5)	803 (4.4)
Grade 3	8 (1.6)	277 (1.5)
Grade 3 or Grade 4	8 (1.6)	277 (1.5)
Fatigue - N1	502	18,167
Any	185 (36.9)	5589 (30.8)
Grade 1	82 (16.3)	3507 (19.3)
Grade 2	89 (17.7)	1766 (9.7)
Grade 3	14 (2.8)	316 (1.7)
Grade 3 or Grade 4	14 (2.8)	316 (1.7)
Myalgia - N1	502	18,167
Any	145 (28.9)	4655 (25.6)
Grade 1	77 (15.3)	2994 (16.5)
Grade 2	57 (11.4)	1401 (7.7)
Grade 3	11 (2.2)	260 (1.4)
Grade 3 or Grade 4	11 (2.2)	260 (1.4)

Solicited Adverse Reaction Category Grade	P303 (N=502)	P301 (N=18,174)
Arthralgia - N1	502	18,167
Any	114 (22.7)	3948 (21.7)
Grade 1	62 (12.4)	2610 (14.4)
Grade 2	42 (8.4)	1137 (6.3)
Grade 3	10 (2.0)	201 (1.1)
Grade 3 or Grade 4	10 (2.0)	201 (1.1)
Nausea/Vomiting - N1	502	18,167
Any	54 (10.8)	1274 (7.0)
Grade 1	44 (8.8)	924 (5.1)
Grade 2	10 (2.0)	270 (1.5)
Grade 3	0	80 (0.4)
Grade 3 or Grade 4	0	80 (0.4)
Chills - N1	502	18,167
Any	100 (19.9)	2114 (11.6)
Grade 1	58 (11.6)	1392 (7.7)
Grade 2	38 (7.6)	612 (3.4)
Grade 3	4 (0.8)	110 (0.6)
Grade 3 or Grade 4	4 (0.8)	110 (0.6)

Abbreviations: CI=Confidence interval; Any=Grade 1 or above; N1=Number of exposed participants who submitted any data for the event.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Within each category of summary, a participant is counted once with the highest toxicity grade within 7 days.
95% CI is calculated using the Clopper-Pearson method.
Source: Study P303 CSR Table 14.3.1.2.1.1, Module 2.7.4 Appendix 1.

Solicited Local Adverse Reactions

Incidence, severity, onset, and duration

In the 50 µg group of Study P303, 374/502 participants (74.5%) reported solicited local ARs within 7 days after injection (Table)0. Most solicited local ARs had onset within 1 to 2 days after injection, and a median duration of 2 days.

The most frequently reported solicited local AR was injection site pain, reported in 371/502 participants (73.9%). Most local ARs were Grade 1 in severity. Grade 3 solicited local ARs were reported for 9/502 participants (1.8%): injection site pain was the most frequent of these, reported for 7/502 (1.4%) participants. A single Grade 4 solicited local AR of injection site pain was reported for 1/502 (0.2%) participant, and this event was reported as Grade 4 on Day 3 and resolved by Day 4.

Solicited Systemic Adverse Reactions

Incidence, severity, onset, and duration

In the 50 µg group of Study P303, 261/502 participants (52.0%) reported solicited systemic ARs within 7 days after injection (Table)0. Most solicited systemic ARs had onset within 1 to 2 days after injection and a median duration of 2 days.

The most frequently reported solicited systemic AR was fatigue (185/502 [36.9%]), followed by headache (167/502 [33.3%]) and myalgia (145/502 [28.9%]). Most systemic ARs were Grade 1 or 2 in severity; Grade 3 events were reported for 29/502 participants (5.8%). No Grade 4 solicited systemic ARs were reported.

Solicited Adverse Reactions by Subgroup

Solicited ARs in Study P303 were assessed by subgroups of age, sex, race, ethnicity, and RSV-LRTD risk factor. No notable differences were observed in the incidence of solicited AR across subgroups of sex, race, or most RSV-LRTD risk factor (specifically CAD/CHF and DM) compared to incidence in the overall 50 µg Safety Set (ie, <10% difference) (Table 10). The incidence of solicited AR by subgroups of age, ethnicity, and the RSV-LRTD risk factor of chronic lung disease showed numeric differences compared to the overall 50 µg Safety Set (ie, >10% difference). The study was not designed to assess differences in these subgroups and the results should be interpreted with caution given that formal tests have not been performed and clinical relevance is not clear.

- Age subgroups: The incidence of solicited local ARs was 88.3% in participants aged 18 to 49 years and 74.5% for the overall group, while the incidence of solicited systemic ARs was 63.8% for participants aged 18 to 49 years and 52.0% for the overall group. No notable differences were observed for participants aged 50 to 59 years compared to the overall 50 µg Safety Set (Table 10).
- Ethnicity subgroups: The incidence of solicited local ARs for participants who reported Hispanic or Latino ethnicity was 56.4% and 74.5% for the overall group, and solicited systemic ARs was 37.9% for participants who reported Hispanic or Latino ethnicity and 52.0% for the overall group (Table 10).
- RSV-LRTD Risk factor subgroups: The incidence of solicited systemic ARs was 62.2% in participants with chronic lung diseases and 52.0% for the overall group (Table)0.

Unsolicited Adverse Events

Summary of Unsolicited Adverse Events

The sections below present unsolicited AEs within 28 days after injection followed by a summary of MAAEs up to Day 181, and SAEs, AESIs, and AEs leading to discontinuation up to DCO (median follow-up of 253 days). Within each section, results for the 50 µg group are presented first, followed by results of the total study population (mRNA-1345 30 µg and 50 µg groups; Study P303 Safety Set). Where insights from review of AE reported in the 30 µg group assist the overall assessment of safety, these results are reviewed.

Unsolicited Adverse Events Within 28 Days After Injection

In the 50 µg group, unsolicited AEs within 28 days after injection were reported in 106/502 (21.1%) participants regardless of Investigator assessment of relationship and 9/502 (1.8%) participants for events considered by the Investigator to be related to study injection (Table 10). MAAE were reported in 53/502 (10.6%) participants for events regardless of relationship and in

2/502 (0.4%) participants for events considered to be related to study injection by the Investigator. A total of 3 events assessed by the Investigator as related to study injection were reported in these 2 participants: muscle tightness, urticaria, and aphthous ulcer; the urticaria event is further discussed in CSR Section 7.5.2 and events of muscle tightness and aphthous ulcer are further discussed in CSR Section 7.6.

No SAEs, fatal events, AEs leading to study discontinuation, or AESIs were reported (regardless of their Investigator-assessed relatedness).

Similarly, in the total study population unsolicited AEs within 28 days after injection were reported in 226/999 (22.6%) participants for events regardless of relationship to the study vaccine and by 17/999 (1.7%) participants for events considered related to the study injection by the Investigator (Table 10). MAAEs were reported in 117/999 (11.7%) participants for events regardless of relationship and in 2/999 (0.2%) participants for events considered related to the study injection by the Investigator. SAEs were reported in 2/497 (0.4%) participants in the 30 µg group; both were considered unrelated to study injection by the Investigator. No fatal events, AEs leading to study discontinuation, or AESIs regardless of their relationship to the study injection as assessed by the Investigator, were reported in in the total study population up to 28 days after injection.

Table 10: Overall Summary of Unsolicited AEs up to 28 Days (P303 Safety Set)

	mRNA-1345 50 µg (N=502) n (%)	Total [a] (N=999) n (%)
Unsolicited AEs up to 28 Days after Injection, Regardless of Relationship to Study Injection		
All	106 (21.1)	226 (22.6)
Serious	0	2 (0.2)
Fatal	0	0
Medically-Attended	53 (10.6)	117 (11.7)
Leading to Study Discontinuation	0	0
Severe/≥ Grade 3	0	2 (0.2)
Any AESI	0	0

	mRNA-1345 50 µg (N=502) n (%)	Total [a] (N=999) n (%)
Unsolicited AEs up to 28 Days after Injection, Related to Study Injection		
All	9 (1.8)	17 (1.7)
Serious	0	0
Fatal	0	0
Medically-Attended	2 (0.4)	2 (0.2)
Leading to Study Discontinuation	0	0
Severe/≥ Grade 3	0	0
At least 1 Non-Serious event [b]	9 (1.8)	17 (1.7)
Severe/≥ Grade 3 [b]	0	0
Any AESI	0	0

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; DCO = Data Cutoff; SAE = serious adverse event.
Up to DCO/End of study: up to DCO or End of study, whichever occurred first.
An adverse event (AE) is defined as any event not present before exposure to study injection or any event already present that worsens in intensity or frequency after exposure.
Severe AEs include both unsolicited severe AEs and ≥ Grade 3 solicited ARs that meet SAE criteria.
Percentages are based on the number of participants in the Safety Set.
[a] Total refers to all participants in the set who received mRNA-1345 50 µg or mRNA-1345 30 µg.
[b] Participants with at least one nonserious AE are included.
Source: Study P303 CSR Table 14.3.2.1.1.1.

Unsolicited Adverse Events within 28 Days After Injection by SOC and PT

The frequently reported unsolicited AEs within 28 days after injection were common infections or were largely associated with reactogenicity. The most frequently reported SOC for these AEs was infections and infestations, in both the 50 µg group and in the total study population. Although there was no placebo arm for comparison in Study P303, in the larger placebo-controlled Study P301, no safety concerns were identified.

Within 28 days after injection, the most frequently reported SOCs (in >1.0%) with the first 2 most frequently reported PTs for the 50 µg group in each SOC were as follows (Module 2.7.4 Section 3.1.2):

mRNA-1345 50 µg Group

- Infections and infestations: 67/502 (13.3%) participants, with upper respiratory tract infection occurring in 16/502 (3.2%) participants, rhinovirus infection and nasopharyngitis, each in 9/502 (1.8%) participants.
- Respiratory, thoracic, and mediastinal disorders: 12/502 (2.4%) participants, including asthma in 4/502 (0.8%) participants and epistaxis, rhinorrhea, and oropharyngeal pain, each in 2/502 (0.4%) participants.
- Musculoskeletal and connective tissue disorders: 9/502 (1.8%) participants, including arthralgia 2/502 (0.4%) and osteoarthritis, muscle spasms, spinal osteoarthritis, limb

discomfort, muscle tightness, sacral pain, spinal pain, and temporomandibular joint syndrome each in 1/502 (0.2%) participants.

- Gastrointestinal disorders 6/502 (1.2%) participants, including diarrhea, constipation, gastrooesophageal reflux disease, nausea, aphthous ulcer, dyspepsia, and gastritis, each in 1/502 (0.2%) participants.
- Skin and subcutaneous tissue disorders: 6/502 (1.2%) participants, including dermatitis contact, purpura, rash, rash macular, rash maculo-papular, and urticaria, each in 1/502 (0.2%) participants.
- Nervous system disorders were reported in 5/502 (1.0%) participants, with dizziness reported in 2/502 (0.4%) participants, and headache, hypoaesthesia, and paraesthesia, each reported in 1/502 (0.2%) participants.

Total Study Population

- Infections and infestations: 142/999 (14.2%) participants, with upper respiratory tract infection and COVID-19 being the most frequently reported PTs, observed in 39/999 (3.9%) participants and 24/999 (2.4%) participants, respectively.
- Musculoskeletal and connective tissue disorders: 22/999 (2.2%) participants, including osteoarthritis in 4/999 (0.4%) participants and arthralgia in 3/999 (0.3%) participants.
- Respiratory, thoracic, and mediastinal disorders: 21/999 (2.1%) participants, with asthma in 5/999 (0.5%) participants and cough, epistaxis, and rhinorrhoea, each in 4/999 (0.4%) participants.
- Gastrointestinal disorders in 14/999 (1.4%) participants, including diarrhea in 4/999 (0.4%) participants and abdominal pain, constipation, gastro-oesophageal reflux disease, and nausea, each in 2/999 (0.2%) participants.
- General disorders and administration site conditions 12/999 (1.2%), including injection site pruritus in 3/999 (0.3%) participants and injection site pain in 2/999 (0.2%) participants.
- Skin and subcutaneous tissue disorders: 11/999 (1.1%) participants including dermatitis contact in 4/999 (0.4%) participants, and eczema, night sweats, purpura, rash, rash macular, rash maculo-papular, and urticaria, each in 1/999 (0.1%) participants.
- Nervous system disorders were reported in 10/999 (1.0%) participants, with headache reported in 3/999 (0.3%) participants, and dizziness and syncope each reported in 2/999 (0.2%) participants.

Unsolicited Adverse Events Up to DCO

In the 50 µg group up to the DCO (cumulative), SAEs were reported in 19/502 (3.8%) participants and MAAEs in 172/502 (34.3%) participants. No AEs leading to study discontinuation or AESIs were reported in the 50 µg group. No fatal events were reported up to DCO in the 50 µg group (Table 11).

In the total study population, up to the DCO (cumulative), SAEs were reported in 56/999 (5.6%) participants. MAAEs were reported in 352/999 participants (35.2%) with 3/999 (0.3%) considered related to study injection. One fatal event (death), which also led to study discontinuation, was reported for a participant in the 30 µg group. Two AESIs were reported (both in the 30 µg group): one participant was reported with an event of seizure, another participant was reported with an

event of Bell's palsy (also reported as an SAE). The AESI of Bell's palsy was also assessed as a MAAE, and was the one SAE up to DCO considered related to study injection by the Investigator.

Table 11: Overall Summary of Unsolicited AEs up to DCO/End of Study (P303 Safety Set)

	mRNA-1345 50 µg (N=502) n (%)	Total [a] (N=999) n (%)
Unsolicited AEs up to DCO/End of Study, Regardless of Relationship to Study Injection		
Serious	19 (3.8)	56 (25.6)
Fatal	0	1 (0.1)
Medically-Attended [b]	172 (34.3)	352 (35.2)
Leading to Study Discontinuation	0	1 (0.1)
Severe/≥ Grade 3	13 (2.6)	38 (3.8)
Any AESI	0	2 (0.2)
Unsolicited AEs up to DCO/End of study, Related to study injection		
Serious	0	1 (0.1)
Fatal	0	0
Medically-Attended [a]	2 (0.4)	3 (0.3)
Leading to Study Discontinuation	0	0
Severe/≥ Grade 3	0	0
Any AESI	0	1 (0.1)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; DCO = data cutoff.
Up to DCO/End of study: up to DCO or End of study, whichever occurred first.
An adverse event (AE) is defined as any event not present before exposure to study injection or any event already present that worsens in intensity or frequency after exposure.
Severe AEs include both unsolicited severe AEs and ≥ Grade 3 solicited ARs that meet SAE criteria.
Percentages are based on the number of participants in the Safety Set.

a. Total refers to all participants in the set who received mRNA-1345 50 µg or mRNA-1345 30 µg.
b. Medically-Attended AEs are summarized up to Day 181/Month 6.
Source: Study P303 CSR Table 14.3.2.1.1.1.

Unsolicited Adverse Events by Severity

In the 50 µg group, up to 28 days after injection, no participants reported severe AEs. Up to DCO, severe AEs were reported in 13/502 (2.6%) of participants in the 50 µg group, none of which were assessed by the Investigator as related to study injection.

In the total study population, up to 28 days after injection, 2/999 participants (0.2%) reported severe AEs, including one event each of pneumonia and asthma. These events were both reported in the 30 µg group and were assessed by the Investigator as serious; neither of these severe AEs up to 28 days after injection were considered related to study injection by the Investigator. Up to DCO, severe AEs were reported in 38/999 (3.8%) of the total study population. None of the severe

AEs reported up to DCO in the total study population were assessed by the Investigator as related to study injection.

Unsolicited Adverse Events Considered Injection-related by the Investigator

In the 50 µg group, unsolicited AEs up to 28 days after injection that were considered related to study injection by the Investigator were reported for 9/502 participants (1.8%), accounting for 11 events (Table 12). No specific AEs by PTs were reported in more than 1 participant in the 50 µg group. All unsolicited AEs up to 28 days after injection that were assessed by the Investigator as related to study injection were mild to moderate in severity. No severe unsolicited AEs up to 28 days after injection were considered to be related to study injection by the Investigator.

In the total study population, unsolicited AEs up to 28 days after injection that were considered by the Investigator to be related to study injection were reported for 17/999 participants (1.7%), accounting for 20 events recorded (Table 12). Most events assessed as related were associated with reactogenicity events (ie, lymph node pain, injection site pain), study procedures (ie, vaccination site bruising), potential nonserious hypersensitivity reactions (ie, urticaria, rash macular, injection site pruritus) or upper respiratory tract infections. No specific AEs assessed as related by PTs were reported in more than 3 participants (0.3%) in the total study population. All unsolicited AEs up to 28 days after injection that were assessed by the Investigator as related to study injection were mild to moderate in severity. No severe unsolicited AEs up to 28 days after injection were considered to be related to study injection by the Investigator in the 50 µg group or the total population.

Table 12: Participant Incidence of Unsolicited Treatment-related AEs up to 28 Days After Injection - by SOC and PT (P303 Safety Set)

System Organ Class Preferred Term	mRNA-1345 50 µg (N=502) n (%)	Total [a] (N=999) n (%)
Number of Participants Reporting Unsolicited Treatment-Related Adverse Events	9 (1.8)	17 (1.7)

System Organ Class Preferred Term	mRNA-1345 50 µg (N=502) n (%)	Total [a] (N=999) n (%)
Number of Unsolicited Treatment-Related Adverse Events	11	20
Infections and infestations	1 (0.2)	2 (0.2)
Rhinovirus infection	1 (0.2)	1 (0.1)
Viral upper respiratory tract infection	0	1 (0.1)
Blood and lymphatic system disorders	0	1 (0.1)
Lymph node pain	0	1 (0.1)
Nervous system disorders	1 (0.2)	1 (0.1)
Dizziness	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)
Rhinorrhoea	0	1 (0.1)
Gastrointestinal disorders	3 (0.6)	5 (0.5)
Diarrhoea	1 (0.2)	3 (0.3)
Aphthous ulcer	1 (0.2)	1 (0.1)
Dyspepsia	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.4)	2 (0.2)
Rash macular	1 (0.2)	1 (0.1)
Urticaria	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	2 (0.4)	2 (0.2)
Muscle spasms	1 (0.2)	1 (0.1)
Muscle tightness	1 (0.2)	1 (0.1)
General disorders and administration site conditions	2 (0.4)	6 (0.6)
Injection site pruritus	1 (0.2)	3 (0.3)
Injection site pain	0	2 (0.2)
Vaccination site bruising	1 (0.2)	1 (0.1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
An adverse event (AE) is defined as any event not present before exposure to study injection or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of participants in the Safety Set.
System Organ Class (SOC) is displayed in an internationally agreed order. Preferred Term (PT) is displayed in descending order of frequency of the Total group and then alphabetically within each SOC.
AEs were coded using MedDRA, version 25.0.
[a] Total refers to all participants in the set who received mRNA-1345 50 µg or mRNA-1345 30 µg.
Source: Study P303 CSR Table 14.3.2.3.1.1.

Unsolicited Adverse Events by Subgroup

In the 50 µg group, unsolicited AEs were reviewed based on subgroups of age, sex, race, ethnicity, and RSV-LRTD risk factor. Results show no clinically meaningful differences or safety concerns in unsolicited AE by study subgroups. No trends were observed indicative of any potential safety

concern. Unsolicited AEs for the 50 µg group are available for the age, sex, race, ethnicity, and RSV-LRTD risk factor (refer to Clinical Overview Module 2.7.4 Section 6.1.2).

Deaths

In the 50 µg group, no deaths were reported (refer to Module 2.7.4 Section 3.1.5).

In the total study population, up to DCO, 1 death was reported for a participant in the 30 µg group. 1 participant with a history of obesity, essential hypertension, COPD, emphysema, obstructive sleep apnea, Type 2 DM, and deep vein thrombosis, died on Day 89. The cause of death was reported as unknown. The event led to study discontinuation and was considered to be unrelated to study injection by the Investigator.

Serious Adverse Events

Up to 28 Days After Injection

In the 50 µg group, no SAEs were reported for participants up to 28 days after injection.

In the total study population, 2/999 participants (0.2%), both in the 30 µg group, reported SAEs within 28 days of study injection. One participant was diagnosed with pneumonia and hospitalized; RSV test was not performed, and no treatment was reported. The event was severe, lasted for 4 days and was considered unrelated to study injection by the Investigator. The other participant experienced an asthma exacerbation that required admission to the Intensive Care Unit for respiratory support. The participant tested positive for SARS-CoV-2 and negative for RSV, received antiviral and antibiotic treatment, and recovered within 10 days. Neither event was considered by the Investigator to be related to study injection. Further details for these cases are provided in Clinical Overview Module 2.7.4 Section 3.1.6.

Up to DCO

In the 50 µg group up to DCO, SAEs were reported for 19/502 participants (3.8%). None were considered by the Investigator to be related to study injection. The most frequently reported events by SOC were events within the SOC of infections and infestations (5/502 participants [1.0%]), and nervous system disorders and injury, poisoning and procedural complications (each reported by 4/502 participants [0.8%]).

In the total population up to DCO, SAEs were reported for 56/999 participants (5.6%), with events most frequently reported within the SOC of infections and infestations (15/999 participants, 1.5%).

One SAE was considered related to study injection by the Investigator: A participant (30 µg group) with a history of hypertension, Type 2 DM, obesity, and migraine presented on Day 43 with a sudden onset of peri-oral paresthesia which spread to the eyes, accompanied by a left facial droop. Symptoms were associated with elevated blood pressure. She was treated with acetylsalicylic acid, prednisone, valacyclovir, and methylprednisolone. The event was resolved on Day 64. The Investigator reported this as a related AESI and SAE of Bell's palsy of moderate intensity. Given the multiple confounding underlying medical conditions and the onset at the upper limit of the 42-day risk window, there was insufficient information to indicate a potential causal association with study injection. As such, the MAH judged this event to be unrelated to mRNA-1345. This is supported by results of Study P301, in which cases of Bell's palsy and facial paralysis reported within the 42-day risk window were balanced in incidence between the mRNA-1345 and placebo groups (mRESVIA Product Information).

All SAEs of pulmonary infections, including cystic fibrosis exacerbations, and asthma exacerbations were reviewed for possible RSV association; none had positive RSV test results reported. Participant narratives for all SAEs are provided in P303 CSR Section 15.

Adverse Events that Led to Discontinuation

Up to 28 Days After Injection

In Study P303 up to 28 days post-injection, no study discontinuations due to AEs were reported.

Up to DCO

In the 50 µg group up to the DCO, no AEs leading to discontinuation were reported.

In the total study population up to DCO, 1/999 participant (0.1%) had a fatal event that led to study discontinuation. This event was reported in a participant in the 30 µg group and is described previously.

Adverse Events of Special Interest (Protocol-defined AESIs and Programmed SMQs)

Adverse events of clinical interest in Study P303 were identified based on medical concepts of potential relevance to vaccines in general and/or mRNA vaccines. The section below is a review of protocol-defined AESIs and programmatic SMQs, assessed based on the following approaches. Using either approach no events of concern were identified.

- Protocol-defined AESIs (Section 2.7.5.8 of the protocol [Appendix 16.1.1]) that were identified as such by the Investigator at the time of reporting by Investigators: Section 5.3.5.1.
- Programmed SMQs (MedDRA v25.0) to assess all reported unsolicited AEs: Section 5.3.5.2. Of note, some events identified within the programmatic SMQ analyses overlap with the protocol-defined AESIs.

No safety concerns were identified by MAH medical review of AESIs and SMQs based on event details and based on clinically relevant risk windows for these events.

Protocol-Defined AESI

Up to 28 Days After Injection

In the total population up to 28 days post-injection, no AESIs were reported after injection.

Up to DCO

In the 50 µg group up to the DCO, no AESIs were reported (Table 13).

In the total study population up to the DCO, 2 AESIs (2/999 [0.2%]) were reported: one event of Bell's palsy (also an SAE) and one event of seizure. Both occurred in the 30 µg group.

The AESI of seizure was reported in a participant with a history of convulsive seizures, epilepsy, Type 2 DM, HIV infection, and cardiovascular diseases who experienced a nonserious event of seizure (verbatim term: worsening of convulsive seizure) with onset on Day 53. He was treated with an increased dose of levetiracetam. The event was moderate in severity, lasted for 3 minutes, resolved on the same day, and was considered unrelated to study injection by the Investigator.

Up to DCO, no events of anaphylactic reaction, CEAC-adjudicated cases of acute myocarditis or acute pericarditis, or thrombocytopenia were reported.

Table 13: Participant Incidence of Unsolicited AEs of Special Interest as Assessed by Investigator up to DCO/End of Study - by SOC and PT (P303 Safety Set)

	mRNA-1345 50 µg (N=502)		Total (N=999)	
System Organ Class Preferred Term	Number of Events	Number of Participants Reporting Events n (%)	Number of Events	Number of Participants Reporting Events n (%)
Nervous system disorders	0	0	2	2 (0.2)
Bell's palsy	0	0	1	1 (0.1)
Seizure	0	0	1	1 (0.1)

Abbreviation: DCO = data cutoff.
Up to DCO/End of study: up to DCO or End of study, whichever occurred first.
Source: Table 14.3.2.11.3.1.

Standardized MedDRA Queries

All reported unsolicited AEs (regardless of Investigator assessment as AESI) were analysed using MedDRA SMQs (narrow and narrow + broad scope analyses). All SMQs (Study P303 CSR Section 4.1.8.3; SAP Section 5.9 [Appendix 16.1.9]), including cardiac arrhythmias, cardiomyopathy, cardiac failure, angioedema, peripheral neuropathy, GBS, demyelination, hypersensitivity, immune mediated/autoimmune disorders, embolic and thrombotic events, ischemic heart disease, central nervous system vascular disorders, non-infectious myocarditis/pericarditis, convulsions, vasculitis, hematopoietic cytopenias, arthritis, hearing and vestibular disorders, thrombophlebitis (analyzed by narrow and narrow/broad scope) and anaphylactic reaction (analyzed by algorithmic approach), were reviewed up to 28 days after injection and up to DCO with no additional safety concerns identified.

No events were identified within the narrow SMQs up to 28 days for the following SMQs: cardiac failure, cardiomyopathy, central nervous system vascular disorders, convulsions, demyelination, embolic and thrombotic events, GBS, hematopoietic cytopenias, non-infectious myocarditis/pericarditis, thrombophlebitis, and vasculitis.

Upon review of the narrow/broad SMQ analyses up to DCO, no additional safety concerns were identified and no events potentially concerning for the protocol-defined AESIs of GBS, ADEM or myocarditis/pericarditis were identified. Overall, most of the events observed within these SMQ analyses occurred in participants with risk factors/confounders, had an alternate etiology, were assessed by the Investigator as unrelated to injection, or there was no temporal clustering or biologic plausibility to suggest a potential causal association with mRNA-1345 administration.

Relevant details from programmatic SMQ analyses by narrow or narrow/broad scope are presented below for both study populations up to the DCO. Full details of the narrow/broad scope queries are included in the Study P303 CSR Section 7.5.2.

- The narrow SMQ for GBS did not identify any events of GBS up to DCO. Up to 28 days after injection, 2/502 (0.4%) participants in the 50 µg group and 3/999 (0.3%) participants in the total study population reported of PTs that are included in the narrow/broad SMQ for GBS: hypoesthesia and paraesthesia (both 50 µg group) and peripheral sensory neuropathy (30 µg group). All events were mild in severity, resolved, and were considered not related to study injection by the Investigator. The reported events did not suggest a

concern for GBS or ADEM. Beyond 28 days up to DCO, no additional events were reported in the narrow/broad GBS SMQ.

- Up to DCO, there were no events reported in the total study population within the narrow non-infectious myocarditis/pericarditis SMQ. Two participants in the total study population (2/999 [0.2%]), both in the 30 µg group, had events reported within the narrow/broad non-infectious myocarditis/pericarditis SMQ, including 1 event of troponin increased and one event of ventricular extrasystoles. Upon review of these cases, both participants had underlying risk factors relevant to the cardiac events, such as hypertension and obesity, and neither of these events was concerning for a case of myocarditis/pericarditis.
- Up to DCO, no events of anaphylaxis or thrombocytopenia were identified.

Medically-attended Adverse Events

Up to 28 Days After Injection

Up to 28 days after injection, MAAEs were reported for 53/502 (10.6%) of participants in the 50 µg group and 117/999 (11.7%) in the total study population. The most frequent events by SOC for MAAEs were in the infections and infestations SOC, in which events were reported for 6.0% of 50 µg group participants and 6.4% of participants in the total study population, and in which the most frequent PT was upper respiratory tract infection (reported for 4/502 [0.8%] and 11/999 [1.1%] of participants, respectively). Up to 28 days after injection, 3 MAAEs (aphthous ulcer, urticaria, and muscle tightness) considered to be related to study injection by the Investigator were reported for 2/502 participants (0.4%) in the 50 µg group.

Up to DCO

Up to DCO (cumulative), MAAEs were reported for 172/502 (34.3%) participants in the 50 µg group and 352/999 (35.2%) participants in the total population.

The most frequent SOC for MAAEs was infections and infestations, in which events were reported for 98/502 (19.5%) participants in the 50 µg group and 212/999 (21.2%) participants in the total study population, and in which the most frequent PT was upper respiratory tract infection (reported for 19/502 [3.8%] and 40/999 [4.0%] of participants, respectively). Up to DCO, MAAEs considered to be related to study injection by the Investigator were reported for 2/502 (0.4%) participants in the 50 µg group and 3/999 (0.3%) participants in the total study population. This includes the 1 participant in the 50 µg group discussed above who had 2 related MAAEs reported, one event each of urticaria and muscle tightness. The one MAAE assessed as related by the Investigator in the 30 µg group was the event of Bell's palsy discussed above.

Pregnancy

Female participants of childbearing potential were eligible to be enrolled in the study as per inclusion criteria. Pregnancy tests were performed, if determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study. During the study, 3 pregnancies were reported, including 1 participant in the 50 µg group (resulting in a healthy male infant delivered via cesarean section at 34 weeks gestation without complications or congenital abnormalities) and 2 participants in the 30 µg group (one resulting in elective termination with no known congenital anomalies; the other ongoing without reported acute illnesses or pregnancy complications as of the DCO, with the estimated due date as February 2025.

Overdose and Dependence Potential

Overdose is unlikely because mRNA-1345 is to be administered by a healthcare professional. The clinical consequence of mRNA-1345 overdose is unknown at this time, and there is no specific antidote for an overdose with mRNA-1345.

No cases of study injection overdose on mRNA-1345 were reported in Study P303.

No studies have been conducted to assess dependence potential; however, based on the mRNA-1345 mechanism of action, the vaccine is not considered to have dependence potential.

Worldwide Marketing Experience

The worldwide registration status is outlined in the Clinical Overview Module 2.2 Introduction section related to this submission.

The worldwide administered doses of mRESVIA in the post-market setting were estimated based on the cumulative global distributed doses as of the data lock on 29 Nov 2024. This estimate was adjusted by applying the proportion of doses administered versus distributed in the US, using the most recent data available from the following two data sources up to 29 Nov 2024. The MAH's internal supply chain data provides daily tracking of dose distribution by product and receiving country. The projected cumulative administrations of mRESVIA doses in the US were derived from IQVIA's NPA data for retail pharmacies nationwide. IQVIA's NPA data are refreshed weekly, and the estimated proportions are subject to updates as uptake patterns in the US evolve and NPA data are updated. The estimated proportion in the US was then applied globally to estimate cumulative doses administered. Based on these assumptions, we estimate that approximately 32,716 to 33,403 doses had been administered worldwide in the post-market setting by 29 Nov 2024.

As of 29 Nov 2024, there were no safety concerns identified from postmarketing experience with mRESVIA.

Safety Summary and Conclusions

Safety data were reviewed for the 50 µg group (n=502) and the total study population (n = 999; 30 or 50 µg of mRNA-1345) from 502 adults ≥18 to ≤59 years at increased risk for RSV-LRTD. As of the DCO (18 Sep 2024), participants had been followed for a median of 253 days following a single dose of mRNA- 1345 vaccine. mRNA-1345 was well-tolerated with no safety concerns identified. Results of the safety assessment of mRNA-1345 in this target population are summarized below with a focus on results from the primary analysis of the 50 µg dose.

- In the 50 µg group most solicited local and systemic AR were Grade 1 or 2 in severity, occurred within 1 to 2 days after injection, and resolved within 2 days after onset. The most frequently reported solicited local AR was injection site pain and the most frequently reported solicited systemic ARs were fatigue, headache, and myalgia.
- While there were some numeric differences in the incidence of solicited ARs between some subgroups (age, ethnicity, and presence of chronic lung disease) and the overall population, in general, these differences were small and the reactogenicity profile remained acceptable and similar across subgroups, thus indicating the generalizability of the results from this study.
- A higher rate of solicited local ARs and a similar rate of solicited systemic ARs were reported for the P303 50 µg group compared to Study P301. Importantly, the low incidence of solicited local and solicited systemic ARs ≥Grade 3 were comparable, with no significant differences observed between the younger and older populations.

- Within 28 days after injection, in the total study population, there were no reports of related SAE, no fatal events, AEs leading to study discontinuation, or AESIs, regardless of relationship to study vaccination.
- Up to DCO, one death was reported in the total study population (30 µg group). The event was considered unrelated to study injection by the Investigator; this was also the one AE leading to study discontinuation.
- SAEs up to DCO were reported for 3.8% of participants in the 50 µg group and for 5.6% of participants in the total study population. One SAE (also an AESI) of Bell's palsy (onset Day 43; 30 µg group) was assessed by the Investigator as related to study injection. Because of the presence of multiple confounding factors and the onset just past the traditional 6-week risk window, insufficient information was available to indicate a potential causal association with study injection and the event was judged unrelated by the Sponsor.
- Review of unsolicited AEs by subgroups of age, sex, race, ethnicity, and RSV-LRTD risk factor identified no potential safety concern.
- No events of anaphylaxis, thrombocytopenia, GBS, or ADEM were reported.
- No CEAC-adjudicated events of acute myocarditis or acute pericarditis were reported.
- No safety concerns or trends were identified from review of programmatic searches by SMQ for medical concepts of theoretical clinical interest for vaccines in general and/or mRNA vaccines. These included but were not limited to anaphylaxis, angioedema, hypersensitivity, peripheral neuropathy, embolic and thrombotic events, immune-mediated and autoimmune disorders, and cardiac arrhythmias including atrial fibrillation.

Review of Study P303 safety data obtained after a median follow-up of 253 days demonstrated that 50 µg of mRNA-1345 was well-tolerated with no safety concerns. Results are consistent with those observed in the large pivotal P301 safety and efficacy study (in adults ≥60 years).

2.5.1. Discussion on clinical safety

Solicited Adverse Reactions

In the 50 µg group of Study P303, 374/502 participants (74.5%) reported solicited local ARs within 7 days after injection. Most solicited local ARs had onset within 1 to 2 days after injection, and a median duration of 2 days.

The most frequently reported solicited local AR was injection site pain, reported in 371/502 participants (73.9%). Most local ARs were Grade 1 in severity. Grade 3 solicited local ARs were reported for 9/502 participants (1.8%): injection site pain was the most frequent of these, reported for 7/502 (1.4%) participants. A single Grade 4 solicited local AR of injection site pain was reported for 1/502 (0.2%) participant, and this event was reported as Grade 4 on Day 3 and resolved by Day 4.

In the 50 µg group of Study P303, 261/502 participants (52.0%) reported solicited systemic ARs within 7 days after injection. Most solicited systemic ARs had onset within 1 to 2 days after injection and a median duration of 2 days.
The most frequently reported solicited systemic AR was fatigue (185/502 [36.9%]), followed by headache (167/502 [33.3%]) and myalgia (145/502 [28.9%]). Most systemic ARs were Grade 1 or

2 in severity; Grade 3 events were reported for 29/502 participants (5.8%). No Grade 4 solicited systemic ARs were reported.

Unsolicited Adverse Events within 28 days after injection

In the total study population unsolicited AEs within 28 days after injection were reported in 226/999 (22.6%) participants for events regardless of relationship to the study vaccine and by 17/999 (1.7%) participants for events considered related to the study injection by the Investigator.

In the 50 µg group, unsolicited AEs within 28 days after injection were reported in 106/502 (21.1%) participants regardless of Investigator assessment of relationship and 9/502 (1.8%) participants for events considered by the Investigator to be related to study injection.

In the 50 µg group, no SAEs, fatal events, AEs leading to study discontinuation, or AESIs were reported (regardless of their Investigator-assessed relatedness) within 28 days after injection.

SAEs were reported in 2/497 (0.4%) participants in the 30 µg group; both were considered unrelated to study injection by the Investigator. No fatal events, AEs leading to study discontinuation, or AESIs regardless of their relationship to the study injection as assessed by the Investigator, were reported in in the total study population up to 28 days after injection.

Unsolicited Adverse Events within 28 Days After Injection by SOC and PT

The frequently reported unsolicited AEs within 28 days after injection were common infections or were largely associated with reactogenicity. The most frequently reported SOC for these AEs was infections and infestations, in both the 50 µg group and in the total study population.

Unsolicited Adverse Events Up to DCO

In the 50 µg group up to the DCO (cumulative), SAEs were reported in 19/502 (3.8%) participants and MAAEs in 172/502 (34.3%) participants. No AEs leading to study discontinuation or AESIs were reported in the 50 µg group. No fatal events were reported up to DCO in the 50 µg group.

In the total study population, up to the DCO (cumulative), SAEs were reported in 56/999 (5.6%) participants. MAAEs were reported in 352/999 participants (35.2%) with 3/999 (0.3%) considered related to study injection. One fatal event (death, see below), which also led to study discontinuation, was reported for a participant in the 30 µg group. Two AESIs were reported (both in the 30 µg group): one participant was reported with an event of seizure, another participant was reported with an event of Bell's palsy (also reported as an SAE). The AESI of Bell's palsy was also assessed as a MAAE, and was the one SAE up to DCO considered related to study injection by the Investigator. Bell's palsy is already included in the SmPC for mRNA-1345.

Up to DCO, severe AEs were reported in 38/999 (3.8%) of the total study population. None of the severe AEs reported up to DCO in the total study population were assessed by the Investigator as related to study injection.

SAEs Up to DCO

Deaths

In the 50 µg group, no deaths were reported.

In the total study population, up to DCO, 1 death was reported for a participant in the 30 µg group. 1 participant with a history of obesity, essential hypertension, COPD, emphysema, obstructive sleep apnea, Type 2 DM, and deep vein thrombosis, died on Day 89. The cause of death was reported as unknown. The event led to study discontinuation and was considered to be unrelated to study injection by the Investigator.

Non-fatal SAEs

In the 50 µg group up to DCO, SAEs were reported for 19/502 participants (3.8%). None were considered by the Investigator to be related to study injection. The most frequently reported events by SOC were events within the SOC of infections and infestations (5/502 participants [1.0%]), and nervous system disorders and injury, poisoning and procedural complications (each reported by 4/502 participants [0.8%]).

In the total population up to DCO, SAEs were reported for 56/999 participants (5.6%), with events most frequently reported within the SOC of infections and infestations (15/999 participants, 1.5%).

One SAE was considered related to study injection by the Investigator: A participant (30 µg group) with a history of hypertension, Type 2 DM, obesity, and migraine presented on Day 43 with a sudden onset of peri-oral paresthesia which spread to the eyes, accompanied by a left facial droop. Symptoms were associated with elevated blood pressure. The Investigator reported this as a related AESI and SAE of Bell's palsy of moderate intensity. The MAH judged this event to be unrelated to mRNA-1345. The MAH concludes the SAE which has been reported as a vaccination related AESI and SAE as unrelated based on the arguments of (1) confounding underlying medical conditions and (2) the onset on day 43 after the upper limit of the 42-day risk window. The change of the relatedness for this SAE of Bell's palsy is disagreed. As the SmPC already includes Bell's palsy this issue will not be further pursued.

Adverse Events that Led to Discontinuation

In the 50 µg group up to the DCO, no AEs leading to discontinuation were reported.

Adverse Events of Special Interest

No safety concerns were identified by medical review of AESIs and SMQs based on event details and based on clinically relevant risk windows for these events.

Medically-attended Adverse Events

Up to 28 days after injection, MAAEs were reported for 53/502 (10.6%) of participants in the 50 µg group and 117/999 (11.7%) in the total study population. The most frequent events by SOC for MAAEs were in the infections and infestations SOC, in which events were reported for 6.0% of 50 µg group participants and 6.4% of participants in the total study population, and in which the most frequent PT was upper respiratory tract infection (reported for 4/502 [0.8%] and 11/999 [1.1%] of participants, respectively).

Up to DCO, MAAEs were reported for 172/502 (34.3%) participants in the 50 µg group and 352/999 (35.2%) participants in the total population.

The most frequent SOC for MAAEs was infections and infestations, in which events were reported for 98/502 (19.5%) participants in the 50 µg group and 212/999 (21.2%) participants in the total study population, and in which the most frequent PT was upper respiratory tract infection (reported for 19/502 [3.8%] and 40/999 [4.0%] of participants, respectively). Up to DCO, MAAEs considered to be related to study injection by the Investigator were reported for 2/502 (0.4%) participants in the 50 µg group and 3/999 (0.3%) participants in the total study population. This includes the 1 participant in the 50 µg group who had 2 related MAAEs reported, one event each of urticaria and muscle tightness. The one MAAE assessed as related by the Investigator in the 30 µg group was the event of Bell's palsy discussed above.

Pregnancy

During the study, 3 pregnancies were reported, including 1 participant in the 50 µg group (resulting in a healthy male infant delivered via cesarean section at 34 weeks gestation without complications or congenital abnormalities) and 2 participants in the 30 µg group (one resulting in elective termination with no known congenital anomalies; the other ongoing without reported acute illnesses or pregnancy complications as of the DCO, with the estimated due date as February 2025.

In summary, the CHMP is of the opinion that the overall safety profile remains unchanged as the analysis of unsolicited ARs did not identify any new safety concerns.

2.5.2. Conclusions on clinical safety

The analysis of unsolicited ARs did not identify a new potential safety concern.

In this light, the CHMP is of the view that there are no new major concerns raised by the safety data in the study Study mRNA-1345-P303 (Part A).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH was requested to submit an updated RMP version (1.1) with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.1 with the following content:

Summary of the safety concerns

Table 14 (from Module SVIII). Summary of the safety concerns

PART II: Module SVIII – Summary of the Safety Concerns

Table 14: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Myocarditis/pericarditis
Missing information	Co-administration with other vaccines Use in immunocompromised individuals Use in individuals with autoimmune or inflammatory disorders Long-term safety Use in pregnancy

Pharmacovigilance plan

Table 15 (from part III.1 of the RMP): On-going and Planned Additional Pharmacovigilance Activities

Study Number,	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due**

Title, and Categories (Status)				Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
mRNA-1345-P101 A Phase 1, Randomized, Observer-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Healthy Younger Adults Aged 18 to 49 Years, Women of Child-Bearing Potential Aged 18 to 40 Years, Healthy Older Adults Aged 65 to 79 Years, Japanese Older Adults Aged	Primary Objectives: • To evaluate the tolerability and reactogenicity of a single injection of up to 5 dose levels of mRNA1345 in younger adults, women of child-bearing potential, and older adults, including Japanese older adults. • To evaluate the tolerability and reactogenicity of 3 injections of the middle dose level of mRNA1345 given 56 days apart in younger adults. • To evaluate the tolerability and reactogenicity of a booster injection of mRNA-1345 given approximately 12 months after the primary injection in older adults. • To evaluate the tolerability and reactogenicity of 3 injections of 2 dose levels of mRNA-1345 given 56 days apart in RSV-seropositive children.	• Myocarditis/ pericarditis • Long term safety	Study initiation:	30 Sep 2020
			Study completion:	15 Jul 2024
			Final study report (paediatrics):	18 Oct 2024
			Final study report (other populations):	Jul 2025

≥60 Years, and RSV-Seropositive Children Aged 12 to 59 Months Ongoing				
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 Ongoing	Primary Objectives: • To evaluate the safety and tolerability of the mRNA1345 vaccine. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.	• Myocarditis/ pericarditis • Longterm safety	Study initiation: Study completion: Final study report:	17 Nov 2021 30 Sep 2025 Jul 2026
mRNA-1345-P302 A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicit	Primary Objectives (Part A): • To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of coadministered RSV	• Myocarditis/ pericarditis • Co-administration with other vaccines • Long term safety	Study initiation:	Part A: 01 Apr 2022 Part B: 27 Jul 2022 Part C: 25 Aug

y of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥50 Years of Age Ongoing	vaccine on the immune response to influenza. Primary Objectives (Part B): • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA1273.214. • To evaluate the effect of coadministered mRNA1273.214 on the immune response to RSV-A. • To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2. Primary Objectives (Part C): • To evaluate the safety and tolerability of a booster dose of mRNA-1345 administered at Year 1 following a primary dose. • To evaluate immune response to RSV-A of a booster dose of mRNA1345 administered at Year 1 following a primary dose. • To evaluate the safety and tolerability of booster dose of mRNA-1345 administered at Year 2 following a primary dose. • To evaluate immune response to RSV-A of a booster dose of mRNA-1345 administered at Year 2 following a primary dose.			2023
			Study completion:	Dec 2024
			Final study report:	Nov 2025
mRNA-1345-P303	Primary Objectives (Part A): • To evaluate the safety and tolerability of mRNA-	• Myocarditis/ pericarditis	Study initiation:	06 Oct 2023

A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults Ongoing	1345. • To evaluate the RSV-A and RSV-B nAb responses to a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with that in high-risk older adults (≥60 years). Primary Objectives (Part B): • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSVB nAb responses to 2 doses of 50 µg mRNA-1345 injection administered 57 days apart in immunocompromised participants ≥18 years of age.	• Use in immunocompromised individuals • Long term safety	Study completion: Final study report:	31 Mar 2026 Feb 2027
mRNA-1345-P902 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA1345 Vaccine for respiratory syncytial virus (RSV) in the United States Planned	Primary Objectives: 1. Describe the utilization of the mRNA-1345 vaccine and mRNA1345 vaccine recipients' characteristics, and estimate incidence rates of safety topics of interest among mRNA-1345 vaccine recipients using large-scale administrative claims data in the US 2. Assess the risk of safety topics of interest using large-scale administrative claims data in the US, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort	• Myocarditis/ pericarditis • Co-administration with other vaccines • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Aug 2024 Dec 2027[1]

	design Secondary Objectives: 1. Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60-64, 6569, 70-74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were coadministered with other nonRSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2. Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the Sponsor or request of regulatory agencies			
mRNA-1345-P903 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World	Primary Objectives: 1. Monitor when and where the mRNA-1345 vaccine is distributed in Europe 2. Describe utilization of the mRNA-1345 vaccine and vaccine recipients' characteristics, and estimate the incidence rates of safety topics of interest among mRNA-1345 vaccine recipients in	• Myocarditis/ pericarditis • Co-administration with other vaccines • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders	Protocol completion: Final report:	Nov 2024 Dec 2028[1]

Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe Planned	Europe 3. Assess the risk of safety topics of interest in Europe, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA1345 vaccine, using a comparative cohort design, when thresholds for sample size requirements are met or deemed necessary by the MAH or regulatory agencies Secondary Objectives: 1. Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60-64, 6569, 70-74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were coadministered with other nonRSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2. Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion	• Long-term safety		

	of the MAH or request of regulatory agencies.			
mRNA-1345-P201 A Phase 2, randomized, observer-blind, placebo-controlled, dose-escalation study to evaluate the reactogenicity, safety, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in pregnant women, and safety, and immunogenicity in infants born to vaccinated mothers. Ongoing	Primary objectives: <u>Maternal participants:</u> • To evaluate the reactogenicity and safety of mRNA-1345 administered during pregnancy. <u>Infant participants:</u> • To evaluate the safety profile in infants born to women vaccinated with mRNA-1345 during pregnancy. Secondary objectives: <u>Maternal participants:</u> • To evaluate the immunogenicity of a single injection of mRNA1345 in pregnant women. <u>Infant participants:</u> • To evaluate RSV antibody levels in infants born to women who receive a single mRNA-1345 injection during pregnancy.	• Use in pregnancy	Study initiation:	Nov 2023
			End of enrolment:	24 Feb 2025
			Study completion:	31 Dec 2026
			Final study report:	Jun 2027

Risk minimisation measures

Table* 16*: *Summary table of pharmacovigilance activities and risk minimisation activities by safety concern by safety concern*

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Myocarditis/ pericarditis	Routine risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Targeted follow-up*

	Additional risk minimisation measures: • *None*	*questionnaire for myocarditis/pericarditis* Additional pharmacovigilance activities: • *mRNA-1345-P101* • *mRNA-1345-P301* • *mRNA-1345-P302* • *mRNA-1345-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*
Co-administration with other vaccines	Routine risk minimisation measures: • *Information that no interaction studies have been performed and that concomitant administration of mRESVIA with other vaccines has not been studied in SmPC Section 4.5* • *Guidance for the individual to tell their doctor, pharmacist or nurse if they are taking, have recently taken or might take any other medicines in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P302* • *mRNA-1345-P902* • *mRNA-1345-P903*
Use in immunocompromised individuals	Routine risk minimisation measures: • *Information that safety and immunogenicity data on mRESVIA are not available for immunocompromised individuals, and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine in SmPC Section 4.4* • *Warning for the individual to talk to their doctor, pharmacist or nurse before they are given mRESVIA if they have a weakened immune system which may prevent them*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*

	from getting the full benefit from mRESVIA in PL Section 2 Additional risk minimisation measures: • *None*	
Use in individuals with autoimmune or inflammatory disorders	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P902* • *mRNA-1345-P903*
Long-term safety	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P101* • *mRNA-1345-P301* • *mRNA-1345-P302* • *mRNA-1345-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*
Use in pregnancy	Routine risk minimisation measures: • *Information that there are no or limited amount of data in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to pregnancy in SmPC Section 4.6 and Section 5.3* • *Guidance that mRESVIA should not*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities:

	be used in women who are pregnant in PL Section 2 • *Guidance for the individual to ask their doctor or pharmacist for advice before they are given this vaccine if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2* Additional risk minimisation measures: • *None*	• *mRNA-1345-P201*

2.6.1. Updated Overall conclusion on the RMP

The changes to the RMP v1.1 are acceptable.

The MAH should take the following points into consideration at the next RMP update:

- The MAH is requested to update the indication of mRESVIA in the Part II - Module SI at the next regulatory opportunity.
- The MAH is also asked to add the following sentence "As a precautionary measure, it is preferable to avoid the use of mRESVIA during pregnancy" (from section 4.6 of the SmPC), into to the pregnancy sections of the RMP (e.g. Tables 32, 33, and 40 of the future consolidated RMP).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC have been updated to reflect the extension of the indication to 18 to 59 years of age with comorbidities that increase the risk of RSV-LRTD. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

RSV is a significant cause of respiratory illness, particularly in adults with certain comorbid medical conditions. These conditions include chronic lung diseases such as COPD and asthma, and chronic

heart diseases like CHF and CAD. Studies over the past 2 decades have solidified RSV as a critical pathogen among these populations, contributing to severe respiratory complications.

3.1.2. Available therapies and unmet medical need

The first RSV vaccines were developed and authorized to prevent RSV-LRTD in adults aged 60 years and older. Subsequently, only one of these vaccines received approval for use in adults aged 18 to 59 years who are at increased risk of RSV-LRTD. The risk of RSV-associated hospitalization in adults 18 to 59 years with certain comorbid medical conditions is comparable to that in older adults without these conditions, highlighting the need for additional vaccine options. Because no approved drugs are currently available to treat RSV, introducing additional vaccine options to prevent RSV-LRTD in adults 18 to 59 years with risk factors remains an important public health need.

3.1.3. Main clinical studies

The submission summarizes data from the Phase 3 Study P303, evaluating tolerability, safety and immunogenicity of mRNA-1345 in adults ≥18 to ≤59 years of age at increased risk for RSV-LRTD. Immunogenicity and safety results are summarized for 502 participants who received 50 µg mRNA-1345 as of 18 Sep 2024, at which time all ongoing participants in Part A had completed at least 180 days of follow-up.

3.2. Favourable effects

The co-primary immunogenicity endpoints were assessed by measuring nAb GMT at Day 29 (against RSV A and RSV-B) after a single dose of 50 µg mRNA-1345 in the Study P303. These were compared to nAb GMT at Day 29 from the Study P301 to determine the GMR. Results met Study P303 non-inferiority criteria for the immunogenicity co-primary endpoints.

3.3. Uncertainties and limitations about favourable effects

Study P303 included 502 subjects which is appropriate to compare immunogenicity but limits the probability to detect rare adverse reactions.

While subjects with defined comorbidities were selected for participation in study P303 immunogenicity in immunocompromised subjects has not yet been determined. However, study P303 Part B is investigating immunogenicity in organ-transplant subjects.

While there were 3 cases of pregnancy during conduct of study P303 the impact on pregnancy or breast-feeding after/during vaccination with mRNA-1345 is currently unknown.

3.4. Unfavourable effects

Compared with the older P301 population, the incidence of solicited local ARs was higher in the younger P303 population. The finding that the incidence of solicited local ARs was higher in the younger P303 population is requested to be included in SmPC section 4.8.

As with all vaccinations common adverse reactions are associated to needle puncture and immune response to the antigen.

3.5. Uncertainties and limitations about unfavourable effects

The populations analysed in studies P301 and P303 differed in their age and in the selection of defined co-morbidities in study P303. It remains unclear whether these differences could bias unfavourable effects.

3.6. Effects Table

Table 17: Effects Table for mRNA-1345 in 18-59 yoa with co-morbidities that increase the risk of RSV-LRTD (data cut-off: 18 Sep 2024)

Effect	Short description	Unit	GMR		Uncertainties / Strength of evidence	References
Favourable Effects						
GMR	GMT P303 compared to GMT P301 (95% CI)					
GMR RSV-A	GMT against RSV-A		1.163 (1.053, 1.285)		ANCOVA model-based GMT	
GMR RSV-B	GMT against RSV-B		1.135 (1.037, 1.242)		ANCOVA model-based GMT	
Unfavourable Effects						
sAR in %	sAR P303 compared to sAR P301		Study P303	Study P301		
	Any solicited adverse reactions (95% CI)		79.1 (75.3, 82.6)	68.1 (67.5, 68.8)		

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titres; sAR = solicited adverse reactions

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Compared with the older P301 population, the incidence, but not the severity, of solicited local ARs was higher in the younger P303 population. No new safety concern has been raised on unsolicited ARs.
On the other hand, results from study P303 demonstrated non-inferiority for the co-primary endpoints of immunogenicity, aiming to infer effectiveness from the older population 60 yoa and older to a younger population 18 to 59 yoa with defined comorbidities that increases the risk for RSV-LRTD.

3.7.2. Balance of benefits and risks

While the incidence, but not the severity, of solicited local ARs was higher in the younger P303 population and no new safety concern has been raised on unsolicited ARs the safety profile of mRNA-1345 in 18 to 59 yoa subjects with defined comorbidities that increases the risk for RSV-LRTD is acceptable.

Although in April 2025 another vaccine has been approved for immunisation against RSV in subjects 18 to 59 yoa with defined comorbidities that increases the risk for RSV-LRTD, inference of vaccine effectiveness for mRESVIA to include this group in the indication is providing an alternative vaccination option with an mRNA-based vaccine.

3.8. Conclusions

The overall B/R for active immunisation for the prevention of LRTD caused by RSV in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV for mRESVIA, based on results from Study mRNA-1345-P303 (Part A) - A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults. As a consequence, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC and the corresponding sections of the Package Leaflet are updated accordingly. The updated RMP Version 1.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA, and IIIB and to the Risk Management Plan are recommended.