EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2026
EMADOC-1700519818-3003237
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

mRESVIA

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

Procedure No. EMA/VR/0000312911

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

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List of abbreviations

Abbreviation	Definition
ADEM	acute demyelinating encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
ARD	acute respiratory disease
bAb	binding antibody(ies)
BMI	body mass index
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease-2019
CSR	clinical study report
DCO	data cutoff
DM	diabetes mellitus
EMA	European Medicines Agency
EoS	end of study
EPAR	European Public Assessment Report
EU	European Union
FDA	United States Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCP	good clinical practice
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular(ly)
IU	international unit
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LRTD	lower respiratory tract disease
MAAE	Medically attended adverse event
MAH	Marketing Authorization Holder
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody(ies)

Abbreviation	Definition
NPA	National Prescription Audit
PASS	Postauthorization Safety Study
PP	per-protocol
PPI	per-protocol immunogenicity
PSUR	Periodic Safety Update Report
PT	preferred term
RMP	Risk Management Plan
RNA	ribonucleic acid
RSI	Request for Supplementary Information
RSV	respiratory syncytial virus
RSV-A	RSV subtype A
RSV-B	RSV subtype B
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard dose
SMQ	Standardized MedDRA Query
SOC	system organ class
SRR	seroresponse rate
US	United States
VE	vaccine efficacy
WOCBP	Women of childbearing potential
yoa	years of age

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 12 November 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

Extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in all adults 18 years of age and older for mRESVIA, based on results from Study mRNA-1345-P101, Study mRNA-1345-P301, Study mRNA-1345-P303 Part A and Study mRNA-1345-P302 Part A and Part B. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted.

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

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the P/0195/2023 agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 were:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	12 November 2025

Timetable	Actual dates
Start of procedure:	29 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	22 January 2026
Joint Rapporteur's updated assessment report circulated on:	19 February 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026
MAH's responses submitted to the CHMP on:	03 March 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 March 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	17 March 2026
CHMP opinion:	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Respiratory Syncytial Virus (RSV) infection is a common cause of acute respiratory illness across all age groups and represents a clinically relevant cause of lower respiratory tract disease (LRTD) in adults. While the highest disease burden is observed in infants and older adults, RSV also contributes substantially to morbidity in younger adult populations. Primary RSV infection occurs nearly universally during infancy; however, reinfections are frequent throughout life, including within the same RSV season, reflecting incomplete and non-sterilising immunity following natural infection.

In adults, RSV infection may lead to LRTD, exacerbation of underlying cardiopulmonary disease and, in severe cases, hospitalisation and death. Although hospitalisation rates increase with age and are highest in adults aged ≥65 years, clinically relevant disease and healthcare utilisation also occur in adults aged 18 to 59 years, including those without major comorbidities.

Claimed therapeutic indication

The claimed therapeutic indication under this variation is the extension of active immunisation with mRESVIA (mRNA-1345) for the prevention of RSV-associated LRTD to include all adults 18 years of age and older, regardless of comorbidity status.

Epidemiology and risk factors

Epidemiological studies from Europe and the United States demonstrate a clear age-related gradient in RSV-associated respiratory hospitalisation rates, with the lowest incidence in adults aged 18 to 49 years and the highest incidence in adults aged ≥65 years. Within the European Union, RSV is

estimated to cause approximately 13,000 respiratory hospitalisations annually among adults aged 18 to 64 years and approximately 145,000 hospitalisations among adults older than 65 years.

Across all adult age groups, the risk of RSV-related hospitalisation is increased in individuals with chronic medical conditions, including chronic obstructive pulmonary disease, asthma, congestive heart failure, coronary artery disease and diabetes mellitus. However, RSV also leads to a substantial burden of outpatient illness, emergency department visits and productivity loss in younger adults. Health economic analyses indicate that adults aged 18 to 59 years account for a considerable proportion of RSV-related primary care consultations, work absenteeism and indirect costs, despite lower hospitalisation and mortality rates compared with older adults.

Certain exposure-related risk factors are particularly relevant in younger adults, including living in households with young children and occupational exposure in healthcare or childcare settings. These populations experience increased risk of RSV infection, healthcare utilisation and work loss, contributing to the overall societal impact of RSV.

Aetiology and pathogenesis

RSV is an enveloped RNA virus belonging to the *Pneumoviridae* family. Infection of the respiratory epithelium can lead to inflammation of the lower airways, resulting in impaired gas exchange and worsening of underlying cardiopulmonary disease. In adults, disease severity is influenced by age and the presence of chronic conditions, but reinfections may still result in clinically significant LRTD due to waning immunity and antigenic variability.

Neutralising antibodies play a central role in protection against RSV disease and higher titers have been associated with reduced risk of LRTD. This provides a biologically plausible rationale for vaccination strategies aimed at boosting RSV-specific immune responses in adults across the age spectrum.

Clinical presentation, diagnosis and prognosis

In adults, RSV infection typically presents with non-specific respiratory symptoms ranging from upper respiratory tract illness to LRTD characterised by cough, dyspnoea and wheezing. Severe disease may necessitate hospitalisation and can be associated with complications such as respiratory failure or exacerbation of cardiovascular disease. Clinical severity of RSV-associated hospitalisation in adults has been reported to be comparable to that of influenza, with similar lengths of stay, rates of invasive mechanical ventilation, complications, readmissions and mortality.

Diagnosis of RSV in adults is often underutilised in routine clinical practice, particularly in those younger than 60 years, leading to underestimation of disease burden. This diagnostic gap contributes to incomplete surveillance data and may delay appropriate infection control measures.

Management

Management of RSV infection in adults is primarily supportive, as no specific antiviral therapy is routinely recommended for this population. Preventive strategies therefore represent the main opportunity to reduce RSV-related morbidity and indirect societal costs in conjunction with healthcare utilisation.

An extension of the indication for mRESVIA to all adults aged ≥18 years would address this unmet medical need by enabling broader protection against RSVLRTD across the adult population. Such an indication provides flexibility for national immunisation programmes to define vaccination strategies

aligned with local public health priorities, including potential vaccination of healthcare workers and individuals in close contact with persons at increased risk of severe RSV disease. This broader preventive approach has the potential to mitigate the overall clinical and societal impact of RSV and to enhance healthcare system resilience during seasonal RSV epidemics.

2.1.2. About the product

mRESVIA (mRNA-1345) is a prophylactic vaccine developed for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV). The vaccine is based on messenger RNA (mRNA) technology and encodes a prefusion-stabilised form of the RSV fusion (F) glycoprotein, a viral surface antigen and a primary target of virus-neutralising antibodies.

Following intramuscular administration, the mRNA is taken up by host cells and translated into the RSV F protein, which is subsequently presented to the immune system. This results in the induction of RSV-specific humoral immune responses, including neutralising antibodies, thereby providing protection against RSV-associated LRTD.

mRESVIA is currently approved in the European Union for active immunisation for the prevention of RSV-LRTD in adults 60 years of age and older, as well as in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV. The present Type II variation seeks to extend the approved indication to include all adults 18 years of age and older, irrespective of comorbidity status, based on clinical efficacy, immunogenicity and safety data generated across the adult age spectrum.

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

The clinical development programme for mRESVIA (mRNA-1345) has been conducted in line with applicable CHMP guidance for vaccines intended for the prevention of infectious diseases in adults and follows a stepwise, evidence-based approach. The programme initially established clinical efficacy, safety and durability of protection in older adults and subsequently extended to younger adult populations using immunogenicity-based bridging, where appropriate.

In preparation for the present Type II variation seeking extension of the indication to all adults 18 years of age and older, the Marketing Authorisation Holder engaged in regulatory interaction with the European Medicines Agency through a pre-submission meeting held on 19 September 2025. The Executive Summary of this meeting is included in the application dossier.

During the pre-submission meeting, the proposed scope of the variation, the overall evidence package and the regulatory rationale for extrapolation to the broader adult population were discussed. In particular, the use of a combined dataset comprising clinical efficacy data in adults aged ≥60 years (Study mRNA-1345-P301), immunobridging data in adults aged 18 to 59 years at increased risk for RSV-LRTD (Study mRNA-1345-P303 Part A) and supportive safety and immunogenicity data from younger, healthy adults (Study mRNA-1345-P101) as well as additional adult populations (Study mRNA-1345-P302 Part A and Part B) was addressed. The approach of inferring effectiveness in adults aged 18 to 59 years without predefined high-risk conditions based on comparable immune responses and a consistent safety profile across studies was outlined and discussed.

The development strategy reflects established regulatory principles for vaccines, whereby immunogenicity endpoints, supported by a clear biological rationale and robust efficacy data in a reference population, may be used to support extrapolation of protection to related populations. Extended follow-up data demonstrating durability of vaccine efficacy over multiple RSV seasons were also considered relevant in the context of the proposed broader indication.

No paediatric indication is sought under the present variation and no paediatric investigation plan-related aspects are therefore addressed in this application. Likewise, the product does not have an orphan designation and no orphan-specific considerations apply.

2.2. Non-clinical aspects

2.2.1. Toxicology

The present Type II variation does not introduce any changes to the toxicological profile of mRESVIA (mRNA-1345). No new toxicology studies were required or submitted and the conclusions of the previously assessed toxicological evaluation remain unchanged and applicable.

2.2.2. Ecotoxicity/environmental risk assessment

The present Type II variation concerns an extension of the approved indication for mRESVIA (mRNA-1345) to include all adults 18 years of age and older and does not involve any changes to the qualitative or quantitative composition, pharmaceutical form, route of administration, manufacturing process or overall use pattern of the product. The conclusions of the ERA as previously evaluated and accepted at the time of the initial marketing authorisation and subsequent variations remain applicable.

No additional ecotoxicity or environmental risk assessment data are required or provided in support of the present application.

2.2.3. Discussion on non-clinical aspects

The present Type II variation is limited to an extension of the approved indication for mRESVIA (mRNA-1345) and does not entail any changes to the non-clinical profile of the product. No new non-clinical studies have been conducted or submitted in support of this application, which was considered acceptable by the CHMP.

Accordingly, the previously assessed and accepted non-clinical data, including pharmacology, toxicology and reproductive toxicity, remain applicable and are considered adequate to support the proposed extension of indication. No new non-clinical issues have been identified.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of respiratory syncytial virus mRNA vaccine (nucleoside modified). Considering the above data, respiratory syncytial virus mRNA vaccine (nucleoside modified) is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This Type II variation is primarily supported by immunogenicity data from the Phase 3 Study mRNA-1345-P303 Part A, demonstrating immunobridging to the efficacy established in Study

mRNA-1345-P301, together with relevant safety data in younger adult populations derived from Studies mRNA-1345-P101 (including women of childbearing potential), mRNA-1345-P302 Parts A and B and mRNA-1345-P303 Part A.

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.

Table 1 Tabular overview of clinical studies

Study ID (Country)	Study design	Study population	Regimen (Participants in the Safety Set)
mRNA-1345-P101 (US)	Phase 1, randomized, observer-blind, placebo-controlled, dose-escalation study to assess the safety, reactogenicity, and immunogenicity of the mRNA-1345 vaccine.	Healthy adults 18 to 49 years of age. Healthy adults 65 to 79 years of age. Healthy adults of Japanese descent ≥60 years of age. WOCBP 18 to 40 years of age.	**18 to 49 years:** Single IM injection: mRNA-1345 50 µg (N=19) mRNA-1345 100 µg (N=20) mRNA-1345 200 µg (N=20) Placebo (N=15) 3 IM injections (Days 1, 57, 113): mRNA-1345 100 µg (N=20) Placebo (N=5) **65 to 79 years:** First IM injection + booster (~12 months later): mRNA-1345 12.5 µg (N=48) mRNA-1345 25 µg (N=48) mRNA-1345 50 µg (N=47) mRNA-1345 100 µg (N=48) mRNA-1345 200 µg (N=48) Placebo (N=59) Subset of single injection groups received identical booster injection **Japanese descent ≥60 years:** Single IM injection: mRNA-1345 100 µg (N=21) Placebo (N=4) **WOCBP 18 to 40 years:** Single IM injection: mRNA-1345 12.5 µg(N=51)

Study ID (Country)	Study design	Study population	Regimen (Participants in the Safety Set)
			mRNA-1345 25 µg (N=49) mRNA-1345 50 µg (N=48) Placebo (N=30)
mRNA-1345-P301 (Global)	Phase 2/3, randomized, observer-blind, placebo-controlled, case-driven pivotal safety and efficacy study	Adults ≥60 years of age with or without underlying medical conditions	<u>Single IM injection:</u> mRNA-1345 50 µg (N=18,245) Placebo (N=18,184)
mRNA-1345-P302 Part A and Part B (US)	Phase 3, randomized, observer-blind, safety, tolerability, and immunogenicity study. **Part A:** Coadministration with seasonal quadrivalent SD influenza vaccine. **Part B:** Coadministration with a COVID-19 vaccine.	Medically stable adults ≥50 years. Randomization stratification by age (50 to 59 years, 60 to 74 years, and ≥75 years).	<u>Part A: 2 IM injections on Day 1</u> mRNA-1345 50 µg+placebo (overall N=249; 50 to 59 years N=110) mRNA-1345 50 µg+SD influenza vaccine (overall N=685; 50 to 59 years N=156) SD influenza vaccine+placebo (overall N=689; 50 to 59 years N=155) <u>Part B: 2 IM injections on Day 1</u> mRNA-1345 50 µg+placebo (overall N=554; 50 to 59 years N=206) mRNA-1345 50 µg+COVID-19 vaccine (overall N=562; 50 to 59 years N=206) COVID-19 vaccine+placebo (overall N=560; 50 to 59 years N=210) On Day 29, participants in Part B received an additional injection of either COVID-19 vaccine or placebo to allow all study participants to receive a seasonal COVID-19 vaccine.
mRNA-1345-P303 Part A (Canada, UK, US)	Phase 3, randomized, double-blind, immunogenicity and safety study.	Adults ≥18 to ≤59 years at increased risk for RSV-LRTD.	<u>Single IM injection:</u> mRNA-1345 50 µg (N=502) mRNA-1345 30 µg (N=497)

2.3.2. Pharmacokinetics

No pharmacokinetics studies have been conducted for this product because pharmacokinetics studies are generally not needed for vaccines, consistent with current guidelines for the clinical evaluation of vaccines.

2.3.3. Pharmacodynamics

Pharmacodynamic studies in the context of vaccines are provided by the immunogenicity assessments that characterise the immune response. Results are presented in the efficacy section.

2.3.4. PK/PD modelling

Not applicable

2.3.5. Discussion on clinical pharmacology

Not applicable

2.3.6. Conclusions on clinical pharmacology

Not applicable

2.4. Clinical efficacy

2.4.1. Main study

mRNA-1345-P303 Part A

Methods

Study mRNA1345-P303 (also referred to as "P303") Part A was designed to support the extrapolation of clinical efficacy of mRNA1345 to adults aged 18 to 59 years through an immunobridging approach.

The study evaluated immune responses following vaccination with mRNA1345 in adults aged 18 to 59 years with prespecified chronic conditions associated with an increased risk of RSVassociated lower respiratory tract disease and compared these responses with those observed in adults aged ≥60 years in the pivotal efficacy Study P301.

The primary methodological objective of Study P303 Part A was to demonstrate noninferiority of RSV neutralizing antibody responses at Day 29 postvaccination in adults aged 18 to 59 years relative to the per-protocol immunogenicity population of Study P301. To ensure the validity of the comparison, analyses were conducted using harmonized immunogenicity endpoints, time points and assay methodologies across studies and were based on predefined analysis sets.

Study P301 served as the reference study for efficacy, providing the clinical context in which the immunogenicity findings from Study P303 Part A were interpreted. Comparative analyses were performed between the respective per-protocol immunogenicity populations to support the immunobridging strategy underpinning the proposed extension of indication.

Treatments

In Study P303 Part A, participants were randomized to receive a single intramuscular dose of mRNA-1345 at either 50 µg or 30 µg. The investigational medicinal product is a lipid nanoparticle (LNP) formulation containing mRNA encoding the RSV F glycoprotein stabilized in the prefusion conformation.

The 50 µg dose was administered as a 0.5 mL suspension for injection and the 30 µg dose as a 0.3 mL suspension, both via intramuscular injection. The concentration of the study vaccine was 0.1 mg/mL. The study intervention was supplied as one vial per kit and prepared, packaged and labelled in accordance with applicable Good Manufacturing Practice, Good Clinical Practice and ICH guidelines.

Two batches of mRNA-1345 (7016823002 and 7016823013) were used during Study P303 Part A. Only immunogenicity and safety data from the 50 µg dose group are considered relevant for the present assessment, as this dose corresponds to the approved dose in adults aged ≥60 years and is the dose proposed for the extension of indication.

Objectives

Study P303 was designed to evaluate the tolerability, safety and immunogenicity of mRNA-1345 in adults aged ≥18 years at increased risk for RSV-associated lower respiratory tract disease (RSV-LRTD). The study comprises two parts; only Part A, conducted in adults aged >18 to <59 years with predefined chronic conditions associated with increased RSV-LRTD risk, is addressed in this assessment report.

The co-primary immunogenicity objectives were to evaluate neutralising antibody responses against RSV-A and RSV-B at Day 29 following administration of a single 50 µg dose of mRNA-1345 and to compare these responses with those observed in the pivotal efficacy Study P301 in adults aged ≥60 years. Vaccine effectiveness in the Study P303 population was inferred by immunobridging to Study P301 based on prespecified non-inferiority criteria.

Secondary objectives included the comparison of seroresponse rates between Study P303 Part A and Study P301, as well as the evaluation of immunogenicity following administration of a lower 30 µg dose of mRNA-1345.

Outcomes/endpoints

The co-primary immunogenicity endpoints of Study P303 Part A were the Day 29 geometric mean titers of neutralising antibodies against RSV-A and RSV-B in participants receiving a single 50 µg dose of mRNA-1345, assessed in the per-protocol population. These endpoints were compared with corresponding Day 29 neutralising antibody titers from the per-protocol immunogenicity population of Study P301 using geometric mean ratios.

Secondary immunogenicity endpoints included seroresponse rates against RSV-A and RSV-B at Day 29, defined as a ≥4-fold increase from baseline (or from the assay lower limit of quantification if baseline titers were below this threshold). Additional secondary and exploratory endpoints included immunogenicity outcomes following the 30 µg dose and the evaluation of persistence of immune responses at Day 181.

Sample size

A total of 1,003 participants were randomised in Study P303 Part A. The sample size was considered adequate to support the evaluation of safety and immunogenicity and to allow immunobridging to the

pivotal Study P301 using prespecified non-inferiority criteria for the co-primary immunogenicity endpoints. No formal hypothesis testing for clinical efficacy was planned in Study P303.

Randomisation

Participants were randomised in a 1:1 ratio to receive a single dose of either 50 µg or 30 µg mRNA-1345. Randomisation was stratified by predefined RSV-LRTD risk groups (CAD/CHF, chronic lung disease, or diabetes mellitus) to ensure a balanced distribution of these conditions across treatment groups. As participants could present with more than one risk factor, assignment to a specific risk group was based on the investigator's clinical judgement.

Blinding (masking)

Study P303 Part A was conducted in a randomised, double-blind manner. Participants, investigators and study personnel involved in the conduct and assessment of the study remained blinded to treatment allocation throughout the blinded phase of the study.

Statistical methods

Immunogenicity analyses were performed based on the data cut-off date of 18 September 2024, with database lock on 1 October 2024. Immunogenicity analyses for Study P303 Part A were conducted using the per-protocol population and were compared with the per-protocol immunogenicity population of Study P301.

For the co-primary immunogenicity endpoints, Day 29 neutralising antibody GMTs against RSV-A and RSV-B in the Study P303 50 µg dose group were compared with those from Study P301 using an analysis of covariance model. The model included log-transformed Day 29 antibody titers as the dependent variable, treatment group as a fixed effect and log-transformed baseline titers as a covariate. Geometric mean ratios and two-sided 95% confidence intervals were derived from the model. Non-inferiority was demonstrated if the lower bound of the 95% confidence interval for the GMR exceeded 0.667, corresponding to a non-inferiority margin of 1.5.

Secondary analyses of seroresponse rates were conducted by comparing the proportion of participants achieving a seroresponse at Day 29 between Study P303 and Study P301. Confidence intervals for seroresponse rates were calculated using the Clopper-Pearson method and differences between studies were estimated using the Miettinen–Nurminen method. Non-inferiority for seroresponse rates was demonstrated if the lower bound of the 95% confidence interval for the difference exceeded -10%.

After completion of non-inferiority testing for the co-primary endpoints, secondary immunogenicity endpoints were evaluated sequentially. Descriptive subgroup analyses were performed as applicable. Persistence of immune responses at Day 181 was assessed descriptively, with additional post hoc comparisons to Study P301.

Results

Primary immunogenicity endpoints

The co-primary immunogenicity objectives of Study P303 Part A were to compare RSV-A and RSV-B neutralising antibody (nAb) responses at Day 29 following a single 50 µg dose of mRNA-1345 with those observed in the pivotal efficacy Study P301. The comparison was performed using nAb geometric mean titers (GMTs) in the P303 Part A PP Set and the P301 PPI Set, expressed as geometric mean

ratios (GMRs). Non-inferiority criteria were met for both RSV-A and RSV-B, with GMRs of 1.163 (95% CI: 1.053; 1.285) and 1.135 (95% CI: 1.037; 1.242), respectively (Table 2.).

The CHMP noted that co-primary immunogenicity endpoints and results were previously assessed in EMA/VR/0000248175. The demonstrated non-inferiority of RSV-A and RSV-B nAb GMTs at Day 29 supports immunobridging to the ≥60 years efficacy population and remains applicable in the present variation.

Secondary immunogenicity endpoints

SRR difference at Day 29

Secondary objectives included comparison of seroresponse rates (SRR) at Day 29 between Study P303 Part A and Study P301. A seroresponse was defined as a ≥4-fold increase from baseline (or from LLOQ if baseline was <LLOQ). Non-inferiority was demonstrated for both RSV subtypes, with SRR differences of 11.8% (95% CI: 7.8; 15.5) for RSV-A and 10.8% (95% CI: 5.9; 15.6) for RSV-B (Table 2.).

The CHMP also noted that the difference at Day 29 met prespecified non-inferiority criteria for both RSV-A and RSV-B, providing supportive evidence for comparable immune responses between studies, as previously concluded in EMA/VR/0000248175.

Table 2 Analysis of RSVA and RSVB nAb Levels and Seroresponse at Day 29, including P303 Part A mRNA1345 50 µg and P301 mRNA1345 50 µg (P303 Part A PP Set and P301 PPI Set)

	P303 Part A N=494	**P301 N=1515**
RSV-A nAb Titer (IU/mL)		
N1	492	1513
Model-Based Day 29 GMT [a]	23,245.01	19,988.17
(95% CI)	(21,326.32, 25,336.34)	(19038.32, 20985.41)
GMR (P303 Part A vs P301) (95% CI)	1.163 (1.053, 1.285)	
SRR n (%) [b]	422 (85.8)	1119 (74.0)
(95% CI) [c]	(82.4, 88.7)	(71.7, 76.2)
SRR Difference (P303 Part A vs P301) (%) 95% CI [d]	11.8 (7.8, 15.5)	
RSV-B nAb Titer (IU/mL)		
N1	489	1511
Model-Based Day 29 GMT [a]	7830.71	6901.15
(95% CI)	(7242.04, 8467.23)	(6602.51, 7213.30)
GMR (P303 Part A vs P301) (95% CI)	1.135 (1.037, 1.242)	
SRR n (%) [b]	329 (67.3)	853 (56.5)

(95% CI) [c]	(62.9, 71.4)	(53.9, 59.0)
SRR Difference (P303 Part A vs P301) (%) 95% CI [d]	10.8 (5.9, 15.6)	

Abbreviations:

ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio (model-based); GMT = geometric mean titer; LLOQ = lower limit of quantification; LS = least square; 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 LLOQ were replaced by 0.5×LLOQ. Values greater than the ULOQ were replaced by the ULOQ.

a. The model-based GMT was estimated on an ANCOVA model. In the ANCOVA model, the log transformed antibody levels at Day 29 postbaseline are treated as a dependent variable, with the study intervention 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 were back-transformed to the original scale for presentation.

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

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

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

Source: Study mRNA1345-P303 CSR (Part A) Table 14.2.1.1.1.1, Table 14.2.2.1.1.1

SRR at Day 29 and ≥2-fold increase analysis

At Day 29, SRRs in Study P303 Part A were numerically higher than those observed in the older P301 population for both RSV-A and RSV-B. As all participants had baseline nAb titers above the LLOQ, an alternative ≥2-fold increase analysis was performed. High proportions of participants in Study P303 Part A achieved a ≥2-fold increase in nAb titers for RSV-A (95.9% [95% CI: 93.8; 97.5]) and RSV-B (89.4% [95% CI: 86.3; 92.0]), exceeding the corresponding proportions for RSV-A (91.1% [95% CI: 89.6; 92.5]) and RSV-B (84.1% [95% CI: 82.2; 85.9]) in Study P301 (cf. Study P303 CSR [Part A], Table 13).

The CHMP was of the views that the additional ≥2-fold increase analysis supports robust vaccine-induced immune responses in the presence of pre-existing RSV immunity and is consistent with conclusions drawn in the prior assessment

Subgroup analyses of immunogenicity (Day 29)

For the purpose of the present assessment report, the evaluation of subgroup analyses of immunogenicity at Day 29 is limited to the prespecified subgroups age and RSV-LRTD risk factor. Other subgroup analyses presented by the MAH (e.g. sex, race, ethnicity or BMI) are not considered critical for the assessment of immunobridging in the context of the proposed extension of indication.

Age

Immunogenicity at Day 29 was evaluated by age subgroups within Study P303 Part A, comparing participants aged 18 to 49 years and 50 to 59 years with the overall P303 Part A 50 µg PP set. In addition, descriptive comparisons were performed with a younger age subset of Study P301 (participants aged 60 to 69 years) to provide a conservative reference population. An overview of the results is presented in Table 3.

Baseline neutralising antibody GMTs against RSV-A and RSV-B were lower in both P303 age subgroups compared with the P301 60 to 69 years subset. Following vaccination, marked increases in nAb titers were observed in all age groups. For RSV-A, GMTs at Day 29 reached 19,158 IU/mL (95% CI: 17,336.35; 21,171.16) in the overall P303 population, with comparable values in the 18 to 49 years (18,977.25 IU/mL [95% CI: 16,201.75; 22,228.21]) and 50 to 59 years (19,271.31 IU/mL [95% CI: 16,930.42; 21,935.87]) subgroups and overlapping 95% confidence intervals with the P301 60 to 69 years subset (22,516.65 IU/mL [95% CI: 20,659.30; 24,540.99]). Similar findings were observed for RSV-B, with Day 29 GMTs of 6,719 IU/mL (95% CI: 6,108.93; 7,390.73) in the overall P303 population and comparable values across age subgroups (18 to 49 years: 6,678.02 IU/mL [95% CI: 5702.91; 7819.85]; 50 to 59 years: 6,745.19 IU/mL [95% CI: 5,982.60; 7,604.98] / 60 to 69 years: 7,456.56 IU/mL [95% CI: 6,857.30; 8,108.20]).

Geometric mean fold rises were numerically higher in Study P303 compared with the P301 60 to 69 years subset; however, CIs partially overlapped between studies. For RSVA, GMFRs ranged from 11.59 (95% CI: 10.25; 13.12) to 13.25 (95% CI: 11.38; 15.43) in the P303 age subgroups compared with 9.75 (95% CI: 8.97; 10.61) in the P301 60 to 69 years subset, while for RSVB GMFRs ranged from 6.31 (95% CI: 5.66; 7.04) to 7.20 (95% CI: 6.21; 8.34) in Study P303 compared with 5.54 (95% CI: 5.14; 5.98) in Study P301. Seroresponse rates at Day 29 were comparable between the P303 age subgroups and aligned with the overall per-protocol population (see Table 3.).

Table 3 Summary of nAb GMT, GMFR, and SRR (nAb Against RSV-A and RSV-B nAb) by Visit and Age Group from Studies P303 (50 µg; PP Set) and P301 (PPI Set)

Test Parameter	**P303 Overall**	**P303 18-49 years**	**P303 50-59 years**	**P301 60-69 years**
Timepoint				
Data Category				
Statistics	**N=494**	**N=189**	**N=305**	**N=619**
RSV-A Neutralizing Antibody 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 Neutralizing Antibody 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; GMFR = geometric mean fold rise; GMT = geometric mean titer; 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; N1 = Number of participants with non-missing data at Baseline and Day 29.

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 GM foldrise, 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 x 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 x LLOQ, or at least a z-fold increase if Baseline is equal to or above the LLOQ.

Source: Study mRNA-1345-P303 CSR (Part A) Table 14

Model-based comparisons further supported these findings. For the comparison between the P303 50 to 59 years subgroup and the P301 60 to 69 years subset, the GMR at Day 29 was 1.017 (95% CI: 0.892; 1.159) for RSVA and 1.036 (95% CI: 0.919, 1.169) for RSVB. Comparable results were observed for the overall P303 population versus the P301 60 to 69 years subset, with GMRs of 1.043 (95% CI: 0.932, 1.169) for RSVA and 1.065 (95% CI: 0.959, 1.183) for RSVB (cf. Study P303 CSR [Part A], Table 15 & Table 16).

The CHMP noted that the age subgroup analyses do not indicate a relevant impact of age on immunogenicity within the adult population aged 18 to 59 years. Neutralising antibody responses at Day 29 were comparable between age subgroups and consistent with those observed in the reference population of Study P301, supporting the applicability of immunobridging across the assessed age range.

RSVLRTD risk factor

Immunogenicity was evaluated in participants with prespecified RSVLRTD risk factors, including CAD/CHF, chronic lung disease and type 1 or type 2 diabetes mellitus. nAb responses within each subgroup were consistent with those observed in the overall 50 µg PP Set, irrespective of the presence of multiple risk factors (Study P303 CSR [Part A], Table 20).

The CHMP is of the view that the consistency of immune responses across RSVLRTD risk factor subgroups supports the robustness of the immunogenicity findings within Study P303 Part A.

Persistence of immune responses at Day 181

Persistence of immunogenicity was assessed at Day 181 in the Study P303 Part A PP Set and compared with the Study P301 PPI Set. Post hoc analyses showed GMRs and SRR differences at Day 181 that would have met non-inferiority criteria for both RSVA and RSVB. GMTs at Day 181 remained elevated compared with baseline, with higher GMFRs observed in Study P303 Part A relative to Study P301 (Study P303 CSR [Part A], Table 4).

Table 4 Analysis of RSV-A and RSV-B nAb Levels and Seroresponse at Day 181 Including P303 Part A mRNA-1345 50 µg and P301 mRNA-1345 50 µg (P303 Part A PP Set and P301 PPI Set)

	P303 Part A N=494	P301 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 (P303 Part A vs P301) (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 (P303 Part A vs P301) (%) 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 (P303 Part A vs P301) (95% CI)	1.153 (1.057, 1.258)	
SRR n (%) [b]	142 (31.2)	277 (19.8)
95% CI [c]	(27.0, 35.7)	(17.7, 22.0)
SRR Difference(P303 Part A vs P301) (%) 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; LS = least square; 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 LLOQ were replaced by 0.5×LLOQ. Values greater than the ULOQ were replaced by the ULOQ.

a. The model-based GMT was estimated on an ANCOVA model. In the ANCOVA model, the log-transformed antibody levels at Day 29 postbaseline are treated as a dependent variable, with the study intervention 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 were back-transformed to the original scale for presentation.

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

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

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

Source: Study P303 CSR (Part A) Table 14.2.1.1.1.3, Table 14.2.2.1.1.3.

Although persistence analyses were not prespecified for formal non-inferiority testing, the CHMP noted that the Day 181 dataset indicates sustained and comparable immune responses up to 6 months postvaccination, consistent with conclusions from the prior variation.

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 5 Summary of Efficacy for trial mRNA-1345-P303 Part A

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 Part A	
Design	Phase 3, randomized, double-blind, immunogenicity and safety study	
	Duration of main phase:	6 months

	Duration of Run-in phase: Duration of Extension phase:		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=1,515
Endpoints and definitions	Primary endpoint	Immunogenicity (GMT)	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	Immunogenicity (SRR)	To further evaluate the immune response to RSV-A nAbs after a single dose of 50µg 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	Immunogenicity (SRR)	To further evaluate the immune response to 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).
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	mRNA-1345-P303 A	mRNA-1345-P301
	Number of subject	492	1,513
	RSV-A nAb GMT	23,245.01	19,988.17
	95% CI	21,326.32; 25,336.34	19,038.32; 20,985.41
	Number of subject	489	1,511
	RSV-B nAb GMT	7,830.71	6,901.15
	95% CI	7,242.04; 8,467.23	6,602.51; 7,213.30
Effect estimate per comparison	RSV-A nAb GMR (P303 A vs P301)	1.163	
	95% CI	1.053; 1.285	

	RSV-B nAb GMR (P303 A vs P301)	1.135	
	95% CI	1.037; 1.242	
Notes	ANCOVA model based GMT and GMR values.		
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability	Treatment group	mRNA-1345-P303 A	mRNA-1345-P301
	Number of subject	492	1,513
	RSV-A nAb SRR (%)	85.8	74.0
	95% CI	82.4; 88.7	71.7; 76.2
	Number of subject	489	1,511
	RSV-B nAb SRR (%)	67.3	56.5
	95% CI	62.9; 71.4	53.9; 59.0
Effect estimate per comparison	RSV-A nAb SRR Difference (%) (P303 A vs P301)	11.8	
	95% CI	7.8; 15.5	
	RSV-B nAb SRR Difference (%) (P303 A vs P301)	1.135	
	95% CI	5.9; 15.6	

2.4.2. Discussion on clinical efficacy

Study mRNA-1345-P303 (P303) Part A was conducted to support the inference of effectiveness of mRNA-1345 in adults aged 18 to 59 years by means of immunogenicity bridging to the pivotal efficacy Study P301 conducted in adults aged ≥60 years. The immunobridging approach and its scientific rationale have been previously assessed in the context of the Type II variation EMA/VR/0000248175 and are considered appropriate.

Immunobridging by demonstration of non-inferiority in terms of the ratio of geometric mean titers (GMR) in adults aged 18 to 59 years from Study P303 compared with adults aged ≥60 years from Study P301 is acceptable to the CHMP. The non-inferiority criteria applied for the immunogenicity co-primary endpoints, namely non-inferiority of GMRs against RSVA and RSVB with a lower bound of the 95% confidence interval ≥0.667, are commonly used and are considered appropriate.

Study P303 Part A evaluated two doses of mRNA1345 at doses of 30 µg and 50 µg. Only data from the 50 µg dose group were considered for the immunobridging analyses, which is acceptable to the Committee. The 50 µg dose is the approved dose in adults aged ≥60 years based on the pivotal Study P301 and is the dose proposed for the extension of indication.

In Study P303 Part A (50 µg cohort), the majority of participants were aged 50 to 59 years, while younger age groups were less represented. This distribution is considered acceptable in the context of immunobridging, as immunogenicity is not expected to be reduced in younger adults compared with older adults and the comparison was anchored to an efficacy population aged ≥60 years.

The co-primary immunogenicity endpoints were assessed by measuring neutralising antibody GMTs at Day 29 against RSV-A and RSV-B following a single 50 µg dose of mRNA-1345 in Study P303 and were compared with corresponding data from Study P301 to determine GMRs. Results met the prespecified non-inferiority criteria. These results were based on ANCOVA model-derived GMT values. Although non-ANCOVA-based GMT values in Study P303 were slightly lower than those observed in Study P301, baseline antibody titers in Study P301 were substantially higher, which explains the observed differences.

Clarification was previously requested regarding the comparability of immunogenicity data between Studies P301 and P303. The MAH confirmed that internal quality control samples were used during immunogenicity testing, which was considered acceptable in the prior assessment (cf. EMA/VR/0000248175).

Non-inferiority in terms of GMR and SRR was also demonstrated at 6 months postvaccination, although this was not a formal endpoint of the study. Analyses of binding antibodies against prefusion F protein further supported the consistency of immune responses between studies.

Secondary immunogenicity endpoints, including SRR differences at Day 29, also met prespecified non-inferiority criteria for both RSV-A and RSV-B. Subgroup analyses did not demonstrate meaningful differences in immune responses by age, sex, race, ethnicity, RSV-LRTD risk factor, or body mass index, although the limited size of some subgroups restricts the interpretability of these analyses.

2.4.3. Conclusions on the clinical efficacy

The immunobridging approach using Study P303 Part A to infer effectiveness of mRNA-1345 in adults aged 18 to 59 years relative to adults aged ≥60 years with established clinical efficacy is considered acceptable by the CHMP.

The non-inferiority criteria applied for the immunogenicity co-primary endpoints are commonly used and appropriate. Results met the non-inferiority criteria for both co-primary and secondary immunogenicity endpoints.

Taken together with the demonstrated clinical efficacy of mRNA1345 in adults aged ≥60 years, the CHMP is of the opinion that the available immunogenicity data support the extension of the indication to all adults aged ≥18 years.

2.5. Clinical safety

Introduction

This section provides an overview of the clinical safety profile of mRNA-1345 in the context of the proposed extension of the indication to adults aged 18 years and older. The established safety profile in the currently approved indication is based on an extensive clinical development programme including more than 18,000 older adults aged 60 years and above exposed to a single 50 µg dose of mRNA-1345 in Study P301, in whom vaccine efficacy was demonstrated and no new or unexpected safety concerns were identified.

For the present variation, the safety database is expanded by data from approximately 2,000 additional participants aged 18 to 59 years. These data derive from Study P303 Part A in adults at increased risk for RSV lower respiratory tract disease, as well as from Studies P101 and P302 Parts A and B in healthy or medically stable adults, including women of childbearing potential and individuals receiving concomitant influenza or COVID-19 vaccination. Safety and reactogenicity outcomes in these younger adult populations are assessed in an integrated manner and interpreted in relation to the established safety profile in older adults, while relevant study specific design features are described where applicable.

Participant population

The clinical safety data supporting the proposed extension of the indication are derived from several studies enrolling adults aged 18 to 59 years, covering a range of clinical settings including healthy individuals, women of childbearing potential, adults with medically stable conditions and adults at increased risk for RSV lower respiratory tract disease.

Study mRNA-1345-P303 Part A enrolled adults aged 18 to 59 years with medical conditions placing them at increased risk for RSV-LRTD. In this study, a total of 999 participants were exposed to mRNA-1345, with approximately equal allocation to the 50 µg and 30 µg dose groups. Both younger adults aged 18 to 49 years and adults aged 50 to 59 years were represented. The median duration of follow-up from vaccination was approximately eight months, with a broad range reflecting ongoing follow-up at the time of data cut-off.

Study mRNA-1345-P101 included healthy adults aged 18 to 49 years and explored a range of dose levels, as well as placebo control. In addition to single-dose cohorts, a smaller number of participants received repeated administrations. A dedicated cohort of women of childbearing potential aged 18 to 40 years was also included, receiving doses up to 50 µg. Across these cohorts, the median follow-up duration was approximately five to six months, allowing for assessment of short- to mid-term safety outcomes.

Study mRNA-1345-P302 Parts A and B enrolled adults aged 50 to 59 years with medically stable conditions and evaluated the safety of mRNA-1345 administered alone or concomitantly with a standard-dose seasonal influenza vaccine (Part A) or a COVID-19 vaccine (Part B). Substantial numbers of participants in this age group were included across the different treatment arms. Median follow-up durations were approximately six to seven months, with comparable observation periods across the coadministration and control groups.

The size and composition of the safety population supporting the extension of the indication to adults aged 18 to 59 years are considered acceptable to the CHMP. The inclusion of relevant subgroups and the use of an integrated safety assessment across studies are in line with the agreements from the pre-submission meeting.

Solicited Adverse Reactions

The applicant presents solicited adverse reaction (AR) data following administration of the licensed single 50 µg dose of mRNA-1345. This variation focuses on data from Studies mRNA-1345-P303 Part A, P101 and P302 Parts A and B for mRNA-1345 administered alone. The data is summarized in Table 5.

Solicited local adverse reactions

In Study P303 Part A, solicited local ARs within seven days after vaccination were reported in 374 of 502 participants (74.5%) receiving mRNA-1345 50 µg, with injection-site pain reported in 371 participants (73.9%). Median onset was one to two days and median duration was two days. Grade 3 local ARs were reported in 9 participants (1.8%) and one Grade 4 event of injection-site pain (0.2%) was reported, resolving within one day.

In Study P101, solicited local ARs were reported in 14 of 19 healthy adults aged 18 to 49 years (73.7%) and in 44 of 48 women of childbearing potential (91.7%). Most events were Grade 1 or 2, with Grade 3 local ARs reported in 1 of 19 healthy adults and 6 of 48 women of childbearing potential. No Grade 4 local ARs were reported.

In Study P302, among participants aged 50 to 59 years receiving mRNA-1345 alone, solicited local ARs were reported in 58 of 110 participants (52.7%) in Part A and 124 of 206 participants (60.2%) in Part B.

Solicited systemic adverse reactions

In Study P303 Part A, solicited systemic ARs within seven days after vaccination were reported in 261 of 502 participants (52.0%), most frequently fatigue, headache and myalgia. Grade 3 systemic ARs were reported in 29 participants (5.8%), with no Grade 4 events.

In Study P101, solicited systemic ARs were reported in 11 of 19 healthy adults aged 18 to 49 years (57.9%) and in 36 of 48 women of childbearing potential (75.0%). Grade 3 systemic ARs were reported in 1 of 19 healthy adults and in 8 of 48 women of childbearing potential.

In Study P302, among participants aged 50 to 59 years receiving mRNA-1345 alone, solicited systemic ARs were reported in 43 of 110 participants (39.1%) in Part A and 106 of 206 participants (51.5%) in Part B.

Solicited adverse reactions by subgroup (Table 6)

Subgroup analyses were performed in Study P303 Part A and Study P302. In Study P303 Part A, no notable differences in the incidence of solicited ARs were reported by sex, race, or most RSV-LRTD risk factors. Higher proportions of solicited local and systemic ARs were reported in participants aged 18 to 49 years compared with those aged 50 to 59 years. In Study P302, the incidence of solicited ARs by age group was reported to be similar across the assessed age categories.

The CHMP was of the opinion that the pattern and frequency of solicited adverse reactions observed in the core safety population (Study P303 Part A) are consistent with expectations for an mRNA vaccine. Reactogenicity is frequent, with Grade 3 to 4 events occurring in the single-digit percentage range. Local reactions are mainly driven by injection-site pain, with severe local reactions reported infrequently. Solicited systemic adverse reactions were reported in approximately half of participants, with Grade 3 events occurring in a small proportion. Women of childbearing potential showed numerically higher rates of solicited local and systemic adverse reactions, including a higher proportion of severe reactions, noting the limited cohort sizes.

Table 6 Summary of Participants With Solicited Adverse Reactions Within 7 Days After mRNA-1345 50 µg Injection in Participants Aged 18 to 59 Years by Toxicity Grade (Solicited Safety Set)

Solicited Adverse Reaction **Category** **Grade**	**P303 Part A** **18 to 59 years**	**P101** **18-49 years**	**P101** **WOCBP**	**P302 Part A** **50-59 years mRNA-1345 alone[a]**	**P302 Part B** **50-59 years mRNA-1345 alone[a]**
	(N=502) **n (%)**	**(N=19)** **n (%)**	**(N=48)** **n (%)**	**(N=110)** **n (%)**	**(N=206)** **n (%)**
Solicited ARs - N1	502	19	48	110	206
Any solicited ARs	397 (79.1)	15 (78.9)	44 (91.7)	70 (63.6)	139 (67.5)
95% CI	75.3; 82.6	54.4; 93.9	80.0; 97.7	53.9; 72.6	60.6; 73.8
Grade 1	200 (39.8)	9 (47.4)	18 (37.5)	44 (40.0)	84 (40.8)
Grade 2	161 (32.1)	5 (26.3)	16 (33.3)	17 (15.5)	46 (22.3)
Grade 3	35 (7.0)	1 (5.3)	10 (20.8)	8 (7.3)	8 (3.9)
Grade 4	1 (0.2)	0	0	1 (0.9)	1 (0.5)
Grade 3 or 4	36 (7.2)	1 (5.3)	10 (20.8)	9 (8.2)	9 (4.4)
Solicited local ARs - N1	502	19	48	110	206
Any solicited local ARs	374 (74.5)	14 (73.7)	44 (91.7)	58 (52.7)	124 (60.2)
95% CI	70.5; 78.3	48.8; 90.9	80.0; 97.7	43.0; 62.3	53.2; 66.9
Grade 1	254 (50.6)	9 (47.4)	27 (56.3)	46 (41.8)	104 (50.5)
Grade 2	110 (21.9)	4 (21.1)	11 (22.9)	8 (7.3)	17 (8.3)
Grade 3	9 (1.8)	1 (5.3)	6 (12.5)	3 (2.7)	3 (1.5)
Grade 4	1 (0.2)	0	0	1 (0.9)	0
Grade 3 or 4	10 (2.0)	1 (5.3)	6 (12.5)	4 (3.6)	3 (1.5)
Solicited systemic ARs - N1	502	19	48	110	206
Any solicited systemic ARs	261 (52.0)	11 (57.9)	36 (75.0)	43 (39.1)	106 (51.5)
95% CI	47.5; 56.4	33.5; 79.7	60.4; 86.4	29.9; 48.9	44.4; 58.5
Grade 1	113 (22.5)	8 (42.1)	12 (25.0)	21 (19.1)	59 (28.6)
Grade 2	119 (23.7)	2 (10.5)	16 (33.3)	17 (15.5)	39 (18.9)
Grade 3	29 (5.8)	1 (5.3)	8 (16.7)	5 (4.5)	7 (3.4)
Grade 4	0	0	0	0	1 (0.5)
Grade 3 or 4	29 (5.8)	1 (5.3)	8 (16.7)	5 (4.5)	8 (3.9)

Abbreviations:

AR = adverse reaction; CI = confidence interval; WOCBP = women of childbearing potential. Any = Grade 1 or above; N = number of participants in Solicited Safety Set; N1 = Number of exposed

Solicited Adverse Reaction	P303 Part A	P101	P101	P302 Part A	P302 Part B
Category	18 to 59 years	18-49 years	WOCBP	50-59 years mRNA-1345 alone[a]	50-59 years mRNA-1345 alone[a]
Grade					
	(N=502)	(N=19)	(N=48)	(N=110)	(N=206)
	n (%)	n (%)	n (%)	n (%)	n (%)

participants who submitted any data for the event; n = number of participants in N1 reporting 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.

[a.] For Study P302 Part A and Part B, table presents solicited ARs reported after Day 1 injection.

Sources: Study P303 CSR (Part A) Table 32, Study P101 CSR Table 13, Study P101 CSR Addendum 2 WOCBP Table 8, Study P302 Parts A and B CSR Table 14.3.1.2.1.1.1 and Table 14.3.1.2.1.2.1.1.

Overall, the solicited adverse reaction data are considered acceptable by the CHMP to support the requested extension of the indication to adults aged 18 years and older. Concerns about comparability of reactogenicity rates across studies were raised by the Committee during the procedure; the MAH satisfactorily provided clarification on the data collection.

Unsolicited Adverse Events/Serious Adverse Events/deaths/other significant events

The applicant reports unsolicited adverse events (AEs) from Studies mRNA-1345-P303 Part A, P101 and P302 Parts A and B, including all dose levels evaluated. Unsolicited AEs up to 28 days after vaccination are summarized in Table 6. and events reported up to end of study or data cut-off are summarized in Table 7. Data are presented for mRNA-1345 administered alone and, in Study P302, also in the context of coadministration with influenza or COVID-19 vaccines.

In Study P303 Part A, unsolicited AEs within 28 days after vaccination were reported in 226 of 999 participants (22.6%), irrespective of causality assessment, with events considered related to vaccination reported in 17 participants (1.7%) (Table 6.). Medically attended adverse events (MAAEs) were reported in 117 participants (11.7%), with two participants (0.2%) experiencing events assessed as related. Serious adverse events (SAEs) within 28 days were reported in two participants (0.2%), none of which were considered related. No deaths, adverse events leading to study discontinuation, or adverse events of special interest (AESIs) were reported within 28 days. The most frequently reported unsolicited AEs were associated with infections, reactogenicity-related symptoms or underlying medical conditions.

In Study P101, among healthy adults aged 18 to 49 years receiving a single dose, unsolicited AEs within 28 days after vaccination were reported in 19 of 59 participants (32.2%), with six participants (10.2%) reporting events assessed as related (Table 6.). No SAEs, deaths, adverse events leading to discontinuation or AESIs were reported up to end of study (Table 7.). In women of childbearing

potential, unsolicited AEs within 28 days were reported in 28 of 148 participants (18.9%), with five participants (3.4%) reporting events assessed as related (Table 6.). One AESI was reported and assessed as not related. In the multiple-dose cohorts of Study P101, unsolicited AEs were reported after each injection, with no deaths, SAEs, adverse events leading to discontinuation, severe AEs, or AESIs reported up to end of study (Table 7.).

In Study P302, among participants aged 50 to 59 years, unsolicited AEs within 28 days after vaccination were reported in 14 of 110 participants (12.7%) receiving mRNA-1345 alone and in 15 of 156 participants (9.6%) receiving coadministration with influenza vaccine in Part A and in 16 of 206 participants (7.8%) receiving mRNA-1345 alone and in 21 of 206 participants (10.2%) receiving coadministration with a COVID–19 vaccine in Part B (Table 6.). No deaths, adverse events leading to discontinuation, or AESIs were reported within 28 days and no SAEs were assessed as related.

Across studies, SAEs reported up to end of study or data cut-off occurred infrequently. In Study P303 Part A, SAEs up to data cut-off were reported in 19 of 502 participants (3.8%) in the 50 µg group and in 37 of 497 participants (7.4%) in the 30 µg group, with one SAE (Bell's palsy) assessed by the Investigator as related in the 30 µg group. In Studies P101 and P302, SAEs up to end of study were reported in small numbers and none were assessed as related to vaccination.

AESIs were reported infrequently across studies. No events of anaphylaxis, Guillain–Barré syndrome, acute disseminated encephalomyelitis, myocarditis, or pericarditis were reported. Standardized MedDRA Query analyses in Studies P303 and P302 did not identify additional safety signals up to data cut-off. Subgroup analyses of unsolicited AEs by age, sex, race, ethnicity and RSV-LRTD risk factors did not reveal trends indicative of clinically relevant differences.

Table 7 Overall Summary of Unsolicited AEs up to 28 Days After Single mRNA-1345 Injection in Participants Aged 18 to 59 Years (Safety Set)

	P303 Part A	P101	P101	Study P302 Part A		Study P302 Part B	
	18-59 years	18-49 years[a]	WOCBP	50-59 years	50-59 years	50-59 years	50-59 years
				mRNA-1345 alone	+ influenza vaccine	mRNA-1345 alone	+ COVID-19 vaccine
	(N=999)	(N=59)	(N=148)	(N=110)	(N=156)	(N=206)	(N=206)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Unsolicited AEs up to 28 days after injection, regardless of relationship to study injection							
All	226 (22.6)	19 (32.2)	28 (18.9)	14 (12.7)	15 (9.6)	16 (7.8)	21 (10.2)
Serious	2 (0.2)	0	0	2 (1.8)	0	0	1 (0.5)
Fatal	0	0	0	0	0	0	0
Medically attended	117 (11.7)	9 (15.3)[a]	19 (12.8)	9 (8.2)	8 (5.1)	4 (1.9)	11 (5.3)
Leading to study discontinuation	0	0	0	0	0	0	0
Severe/≥ Grade 3	2 (0.2)	0	1 (0.7)	2 (1.8)	0	0	1 (0.5)
Any AESI	0	0	1 (0.7)	0	0	0	0
Unsolicited AEs up to 28 days after injection, related to study injection							
All	17 (1.7)	6 (10.2)	5 (3.4)	1 (0.9)	1 (0.6)	1 (0.5)	2 (1.0)
Serious	0	0	0	0	0	0	0
Medically attended	2 (0.2)	0	4 (2.7)	0	0	0	0
Severe/≥ Grade 3	0	0	0	0	0	0	0
Any AESI	0	0	0	0	0	0	0

Abbreviations:

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; WOCBP = women of childbearing potential.

This table includes unsolicited AEs reported up to 28 days after a single mRNA-1345 injection at any dose level in each study. For Study P302, the table includes unsolicited AEs reported up to 28 days after Day 1 mRNA-1345 injection in the mRNA-1345 alone and coadministration groups.

An 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 adverse reactions that met seriousness criteria.

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

[a] For Study P101-healthy adults 18 to 49 years, tabulated summaries of unsolicited AEs after the first injection include all AEs up to 28 days post-injection as well as all serious AEs, medically

attended AEs, fatal AEs, and AESIs up to end of study. MAAEs within 28 days after mRNA-1345 injection were reported in 1 participant in the 200 µg group (Study P101 CSR, Listing 16.2.7.7.1).

Sources: Study P303 CSR (Part A) Table 34, Study P101 CSR Table 18, Study P101 CSR Addendum 2 WOCBP, Table 11 and Table 14.3.1.4.3, Study P302 Parts A and B CSR, Table 14.3.2.1.1.1.1 and Table 14.3.2.1.1.2.1.

Table 8 Overall Summary of Unsolicited AEs Up to EoS/DCO in Participants Aged 18 to 59 Years (Safety Set)

	P303 Part A	P101	P101	Study P302 Part A		Study P302 Part B	
	18-59 years	18-49 years[a]	WOCBP	50-59 years	50-59 years	50-59 years	50-59 years
				mRNA-1345 alone	+ influenza vaccine	mRNA-1345 alone	+ COVID-19 vaccine
	(N=999)	(N=59)	(N=148)	(N=110)	(N=156)	(N=206)	(N=206)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Unsolicited AEs up to EoS/DCO, regardless of relationship to study injection							
Serious	56 (5.6)	0	1 (0.7)	3 (2.7)	5 (3.2)	5 (2.4)	4 (1.9)
Fatal	1 (0.1)	0	0	0	0	0	0
Medically attended	352 (35.2)	9 (15.3)	43 (29.1)	20 (18.2)	27 (17.3)	37 (18.0)	39 (18.9)
Leading to study discontinuation	1 (0.1)	0	0	0	0	0	0
Any AESI	2 (0.2)	0	1 (0.7)	0	0	2 (1.0)	1 (0.5)
Unsolicited AEs up to EoS/DCO, related to study injection							
Serious	1 (0.1)	0	0	0	0	0	0
Fatal	0	0	0	0	0	0	0
Medically attended	3 (0.3)	0	4 (2.7)	0	0	0	0
Leading to study discontinuation	0	0	0	0	0	0	0
Any AESI	1 (0.1)	0	0	0	0	0	0

Abbreviations:

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; DCO = data cutoff; EoS = end of study; WOCBP = women of childbearing potential.

This table includes unsolicited AEs reported up to EoS for Studies P101 and P302 and up to DCO for Study P303 Part A.

An 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 were based on the number of participants in the Safety Set.

Sources: Study P303 CSR (Part A) Table 35, Study P101 CSR Table 18, Study P101 CSR Addendum 2 WOCBP, Table 11 and Table 14.3.1.4.3, Study P302 Parts A and B CSR, Table 14.3.2.1.1.1.1 and Table 14.3.2.1.1.2.1.

Overall, the unsolicited adverse event profile observed across Studies P303, P101, P302 and the supportive data from P301 are consistent with the established safety profile of mRNA-1345. Unsolicited AEs, SAEs, AESIs, medically attended adverse events and discontinuations due to AEs were reported at low frequencies, with no new or unexpected safety signals identified. The types and patterns of events were comparable across studies, dose groups, age strata and coadministration settings and align with the known safety experience in older adults.

In this context, the CHMP was of the opinion that the unsolicited adverse event data are considered acceptable to support the requested indication extension.

Safety in special populations

Pregnancy outcomes were reported in a limited number of participants across the clinical development programme. No pregnancies occurred in Study P101 among healthy adults aged 18 to 49 years or in Study P302 Parts A and B.

In Study P303 Part A, women of childbearing potential were enrolled and pregnancy testing was performed during study participation. Three pregnancies were reported during the study period: one in the 50 µg group and two in the 30 µg group. In the 50 µg group, 1 participant had a positive pregnancy test and subsequently delivered by cesarean section. No maternal or neonatal complications were reported and no congenital abnormalities were observed at birth. In the 30 µg group, one participant had a positive pregnancy test; the pregnancy was electively terminated. A second participant in the 30 µg group had a positive pregnancy; the pregnancy was ongoing at the time of data cut-off, with no complications reported.

In the Study P101 women of childbearing potential cohort, two pregnancies were reported. In the 25 µg group, a participant had a positive pregnancy test and subsequently elected to terminate the pregnancy; no further information was available. In the 50 µg group, a participant had a positive pregnancy test and delivered a full-term infant by vaginal delivery. No complications during pregnancy or delivery were reported and no abnormalities were observed at birth or at one month postpartum.

Overall, the limited number of pregnancy cases and the heterogeneity of outcomes do not allow conclusions on the safety of mRNA-1345 during pregnancy. Safety in pregnancy has therefore not been established. The CHMP noted that a dedicated Phase 2 maternal immunization study (Study mRNA-1345-P201) is ongoing and mRNA-1345 is not recommended for use during pregnancy, as reflected in SmPC section 4.6.

Discontinuation due to adverse events

In Study mRNA-1345-P303 Part A, no study discontinuations due to adverse events were reported up to 28 days after injection. In the 50 µg group, no AEs leading to discontinuation were reported up to the data cut-off. In the overall study population, one participant (0.1%) in the 30 µg group discontinued due to a fatal event.

In Study mRNA-1345-P101, no treatment-emergent adverse events (TEAEs) leading to study discontinuation were reported up to end of study among participants who received a single injection of mRNA-1345 at any dose level or placebo.

In Study mRNA-1345-P301, discontinuations due to TEAEs were infrequent and balanced between the mRNA-1345 and placebo groups both up to 28 days after injection (each <0.1%) and up to data cut-off (0.5% in the mRNA-1345 group and 0.6% in the placebo group). Most discontinuations in both groups were associated with fatal TEAEs. Up to 28 days after injection, TEAEs leading to discontinuation were reported in two participants in the mRNA-1345 group and in eleven participants in the placebo group.

In Study mRNA-1345-P302 Part A, no TEAEs leading to study discontinuation were reported up to 28 days after injection. Up to end of study, discontinuations due to TEAEs were reported in three participants (0.4%) in the mRNA-1345 plus influenza vaccine group and in one participant (0.1%) in the influenza vaccine alone group. All discontinuations were due to fatal events.

In Study mRNA-1345-P302 Part B, no TEAEs leading to study discontinuation were reported up to 28 days after injection. Up to end of study, one participant (0.2%) in the mRNA-1345 alone group discontinued due to a fatal event and one participant (0.2%) in the mRNA-1345 plus COVID-19 vaccine group discontinued study injections due to an event of influenza.

Post marketing experience

According to the applicant, no safety concerns had been identified from post-marketing experience with mRESVIA as of the data lock point (30 May 2025). Post-marketing safety surveillance is ongoing through routine pharmacovigilance activities in accordance with the risk management plan.

While the extent of post-marketing exposure remains limited, the CHMP is of the opinion that the ongoing pharmacovigilance activities and dedicated post-marketing studies (including Studies mRNA-1345-P902 and mRNA-1345-P903) are in place to monitor for potential new adverse reactions.

2.5.1. Discussion on clinical safety

The clinical safety assessment for the proposed extension of the indication to adults aged 18 years and older is based on an integrated evaluation of clinical studies enrolling adults aged 18 to 59 years, together with the established safety database in adults aged 60 years and older. The analysis focuses on identifying any new safety concerns arising in the younger adult population, including relevant subgroups such as individuals at increased risk for RSV-LRTD, women of childbearing potential and subjects receiving concomitant vaccinations.

Overall, the reactogenicity profile in adults aged 18 to 59 years is consistent with that observed in older adults and with expectations for an mRNA vaccine. Solicited local and systemic adverse reactions were mainly injection-site pain, fatigue, headache and myalgia, with most events being mild to moderate and transient. Grade 3 reactions occurred in a small proportion of participants and Grade 4 events were rare. Numerically higher reactogenicity rates were observed in women of childbearing potential and in younger adults within the 18 to 49 year age range, without indication of a qualitatively different safety profile.

Unsolicited adverse events, serious adverse events, adverse events of special interest, medically attended adverse events and discontinuations due to adverse events were reported infrequently across studies. No new or unexpected safety signals were identified, including for adverse events of particular relevance to mRNA vaccines such as anaphylaxis, myocarditis, pericarditis, Guillain–Barré syndrome, acute disseminated encephalomyelitis or thrombocytopenia. Standardized MedDRA Query analyses did not reveal additional safety concerns and the overall pattern of unsolicited adverse events was comparable to that in the older adult population.

Pregnancy exposures were limited and occurred inadvertently. The available data do not allow conclusions on safety during pregnancy, which remains unestablished and is appropriately reflected in SmPC section 4.6. A dedicated maternal immunization study is ongoing to further characterise safety in this population. Post-marketing exposure remains limited to date, with no new safety concerns identified and ongoing pharmacovigilance and post-marketing studies are in place.

Concerns about comparability of reactogenicity rates across studies were raised during the procedure; the CHMP requested the MAH to clarify differences in observation windows for solicited adverse reactions between studies (particularly between Study P302 and Studies P303/P101) and how such differences may affect comparability of reactogenicity rates. The MAH satisfactorily addressed this issue.

Besides, no new safety concerns specific to the expanded adult population have been identified and ongoing post-authorisation activities are expected to further inform the safety profile.

2.5.2. Conclusions on clinical safety

No new safety concerns have been identified in adults aged 18 to 59 years in relation to the established safety profile of mRNA-1345. The safety findings in the expanded adult population are consistent with those observed in older adults and with the known reactogenicity and adverse event profile of mRNA vaccines. In particular, no new or increased risks were identified for serious adverse events or adverse events of special interest.

Safety in pregnancy has not been established. The limited and inadvertent pregnancy exposures reported do not allow conclusions and this remains appropriately reflected in the SmPC.

Ongoing and planned post-marketing activities (including routine pharmacovigilance and dedicated post-authorisation studies) are considered appropriate to the CHMP, to further characterise the safety profile, particularly with regard to rare events and special populations such as pregnant women. These data are considered suitable to be generated post-authorisation.

In this light, the CHMP is of the view that the safety data does not raise any new major concerns in support of the requested extension of the indication to adults aged 18 years and older.

No additional safety-related measures are identified as conditions to be included in Annex II at this stage.

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 (5.1) 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 5.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

Table 9 Module SVIII. Summary of the safety concerns

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

Pharmacovigilance plan

Table 10 (from part III.1 of the RMP): On-going and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories (Status)	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due 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-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 (Part A):** • To evaluate the safety and tolerability of the mRNA-1345 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. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose. • To demonstrate noninferiority of the serum RSV-A nAb response of a BD	• Myocarditis/ pericarditis • Long-term safety	Study initiation: Study completion: Final study report:	17 Nov 2021 28 Jul 2025 Jul 2026

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	of mRNA-1345 compared with a primary dose. • To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.			
mRNA-1345-P302 A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥50 Years of Age Ongoing	**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 vaccine on the immune response to influenza. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214. • To evaluate the effect of coadministered mRNA-1273.214 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 BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• Myocarditis/ pericarditis • Long term safety	Study initiation: Study completion: Final study report:	Part A: 01 Apr 2022 Part B: 27 Jul 2022 Part C: 25 Aug 2023 08 Nov 2024 Mar 2026
mRNA-1345-P303 A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults Ongoing	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of mRNA-1345. • 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). **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSV-B nAb GMTs after 2 doses of 50 µg	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Long term safety	Study initiation: Study completion: Final study report:	06 Oct 2023 31 Mar 2026 Feb 2027

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	mRNA-1345 injection administered 56 days apart in participants ≥18 years of age who received SOT.			
mRNA-1345-P902 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in the United States Ongoing	**Primary Objectives:** 1) Describe the utilization of the mRNA-1345 vaccine and mRNA-1345 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 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 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV 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.	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Aug 2024 Dec 2027 [a]
mRNA-1345-P903 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe	**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 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	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Nov 2024 Dec 2028 [a]

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Ongoing	have not received the mRNA-1345 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 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV 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 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 mRNA-1345 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: End of enrolment: Study completion: Final study report:	Nov 2023 24 Feb 2025 31 Dec 2026 Jun 2027

[a] The study period may be extended depending on vaccine uptake to allow for a reasonable sample size to monitor rare Safety Topics of Interest.

Risk minimisation measures

Table 11 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* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Targeted follow-up questionnaire for myocarditis/pericarditis* Additional pharmacovigilance activities: • *mRNA-1345-P301* • *mRNA-1345-P302* • *mRNA-1345-P303* • *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 from getting the full benefit from mRESVIA 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-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*
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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • *None*	• *None* Additional pharmacovigilance activities: • *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 as a precautionary measure, it is preferable to avoid the use of mRESVIA during pregnancy in SmPC Section 4.6* • *Guidance that mRESVIA should not 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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P201*

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated to reflect the extension of the indication to all adults ≥18 years of age. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable by the CHMP for the following reasons:

- The previously submitted user testing report remains applicable, as the original readability testing intentionally included adults aged 18 to 59 years in anticipation of a potential extension of the indication to younger adults.
- The testing methodology covered a broad adult age range and included participants representative of the population eligible under the extended indication, with no age-specific comprehension issues identified.
- All predefined success criteria were met across age groups, supporting the readability and understandability of the package leaflet for the full adult population.
- The proposed package leaflet changes related to the indication extension are minimal and limited to content updates in sections 1 and 2, without any changes to layout or overall structure.

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

Besides mRESVIA, there are 2 vaccines approved in the EU for the prevention of RSV-LRTD in adults. Despite these options, RSV continues to cause a substantial burden of disease across all adult age groups, leading to hospitalizations, medical visits, and productivity losses. Severe outcomes are most frequent among older adults and those with chronic medical conditions. Vaccination of young healthy adults might still be relevant to protect others with increased risk of RSV infection (individuals with immunosuppressed family members, healthcare professionals etc.).

3.1.3. Main clinical studies

3.2. Favourable effects

The favourable effects supporting the proposed extension of indication are primarily derived from immunogenicity data generated in Study P303 Part A. The coprimary immunogenicity objective of demonstrating non-inferiority to older adults (≥60 years) enrolled in the pivotal efficacy Study P301 was met. At Day 29 post vaccination, GMTs of neutralising antibodies against RSV-A and RSV-B in adults aged 18 to <60 years were non-inferior to those observed in the efficacy cohort of Study P301. The reported geometric mean ratios were 1.163 (95% CI: 1.053; 1.285) for RSV-A and 1.135 (95% CI: 1.037; 1.242) for RSV-B.

Subgroup analyses in Study P303 Part A indicated consistent immune responses across predefined demographic and clinical subgroups, including age strata (18 to 49 years and 50 to 59 years), sex, race, ethnicity and BMI.

Durability of the immune response was assessed through persistence analyses in Study P303 Part A up to Day 181 and through extended follow-up in Study P301 with a median follow-up duration of 18.8 months. At six months post vaccination, neutralising antibody responses in younger adults remained elevated above baseline and non-inferior to those observed in older adults in Study P301.

3.3. Uncertainties and limitations about favourable effects

The favourable effects for the proposed indication extension are based exclusively on immunological surrogate endpoints. No direct clinical efficacy data on prevention of RSV-associated lower respiratory tract disease are available for the younger adult population included in Study P303 Part A. The benefit for this population is therefore inferred through an immunobridging approach to older adults in Study P301.

Comparability between the populations of Studies P303 Part A and P301 is subject to uncertainty, as the studies differ with respect to age distribution and underlying risk factors, which may influence baseline immunity and immune responses. Subgroup analyses were exploratory in nature and not powered to detect differences between subgroups.

While persistence data demonstrate sustained antibody responses over time, the clinical relevance of the observed antibody levels and their correlation with long-term protection against RSV disease in younger adults remain uncertain.

3.4. Unfavourable effects

Across the clinical development programme, reactogenicity following vaccination with mRNA-1345 was generally reported as mild to moderate in intensity and transient. Local reactions occurred more frequently in younger adults than in older adults, without evidence of increased severity. Systemic reactions were generally comparable across age cohorts.

No safety concerns specific to younger adults were identified and the overall safety profile of mRNA-1345 was reported as consistent across studies, populations and vaccine administration contexts, including stand-alone use and coadministration with other vaccines.

Review of Investigator-reported adverse events of special interest and programmatic standardised MedDRA queries (including those related to cardiac arrhythmias, demyelinating disorders and peripheral neuropathy) did not identify safety concerns as of the data cut-off. No events met case definitions for anaphylaxis, Guillain-Barré syndrome or acute disseminated encephalomyelitis across the studies included in the clinical overview.

Within the clinical programme, no relevant cases of Bell's palsy were reported in healthy adults aged 18 to 59 years. One case occurred in a participant with relevant comorbidities who received the 30 µg dose in Study P303 Part A. The event was assessed by the Investigator as related and occurred just beyond the predefined six-week risk window, with several confounding medical factors identified.

No cases of myocarditis or pericarditis were reported in Study P303 Part A or in other studies included in the submission.

3.5. Uncertainties and limitations about unfavourable effects

The CHMP was of the opinion that differences in the definition of observation windows between studies (specifically Study P302 versus Studies P303/P101, 'after Day 1 injection' versus 'within 7 days') may impact the comparability of reactogenicity rates and potentially lead to an underestimation in Study P302, as peak reactogenicity typically occurs on Day 1. In response, the MAH provided satisfactory clarifications regarding the diary collection window applied in Study P302.

The mRNA-1345 clinical development programme is not powered to detect very rare adverse events and the available safety database does not allow robust conclusions regarding the incidence of uncommon or very rare risks. In addition, long-term safety data in younger adults are currently limited.

Safety in pregnancy has not been established. With the proposed extension of indication to adults aged ≥18 years, which includes women of childbearing potential, use during pregnancy remains missing information due to limited available data.

Long-term safety follow-up in younger adults is ongoing, with two-year follow-up planned in Study P303. Further characterisation of long-term safety and rare adverse events is intended through post-authorisation safety studies and ongoing post marketing surveillance, including Studies P902 and P903.

3.6. Effects Table

Table 12 Effects Table for mRNA-1345, indicated for the active immunisation for the prevention of RSV-LRTD in all adults 18 years of age and older (data cut-off: 18 September 2024)

Effect	Short description	Unit	Treatment (18 - 59 yoa)	Control (≥60 yoa)	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment (18 - 59 yoa)	Control (≥60 yoa)	Uncertainties / Strength of evidence	References
RSV-A nAb (D29)	RSV-A neutralising antibody response at Day 29	GMT (95% CI)	23,245.01 (21,326.32; 25,336.34)	19,988.17 (19,038.32; 20,985.41)	**SoE:** Primary immunobridging endpoint; non-inferiority met with point estimate >1 and CI excluding 1 **Unc:** Surrogate endpoint; no direct clinical efficacy data in the younger adult population; cross-study comparison (different populations).	P303 Part A; P301
		GMR	1.163 (1.053; 1.285)			
RSV-B nAb (D29)	RSV-B neutralising antibody response at Day 29	GMT	7,830.71 (7,242.04; 8,467.23)	6,901.15 (6,602.51; 7,213.30)	**SoE:** Primary immunobridging endpoint; non-inferiority met with consistent directionality to RSV-A. **Unc:** Same surrogate and cross-study limitations as above.	P303 Part A; P301
		GMR	1.135 (1.037; 1.242)			
RSV-A SR (D29)	RSV-A seroresponse at Day 29	SRR (95% CI)	85.8% (82.4; 88.7)	74.0% (71.7; 76.2)	**SoE:** Consistent supportive endpoint (higher SRR in younger adults) **Unc:** SRR definition and its relation to clinical protection; multiplicity and supportive nature relative to primary endpoint.	P303 Part A; P301
		ΔSRR (95% CI)	11.8% (7.8; 15.5)			
RSV-B SR (D29)	RSV-B seroresponse at Day 29	SRR (95% CI)	67.3% (62.9; 71.4)	56.5% (53.9; 59.0)	**SoE:** see above **Unc:** see above	P303 Part A; P301
		ΔSRR (95% CI)	10.8% (5.9; 15.6)			
Unfavourable Effects						

Effect	Short description	Unit	Treatment (18 - 59 yoa)	Control (≥60 yoa)	Uncertainties / Strength of evidence	References
Solicited ARs	Local, within 7 days (any grade)	n (%)	**P303 Part A:** 374 (74.5) **P101:** 14 (73.7) **P101 WOCBP:** 44 (91.7) **P302 Part A:** 58 (52.7) **P302 Part B:** 124 (60.2)		**SoE:** Standard solicited collection with toxicity grading **Unc:** Heterogeneous populations (healthy, WOCBP, high-risk) and designs; P302 solicited ARs are reported after Day 1 injection only; small N in P101.	P101; P302 Part A & B; P303
	Systemic, within 7 days (any grade)	n (%)	**P303 Part A:** 261 (52.0) **P101:** 11 (57.9) **P101 WOCBP:** 36 (75.0) **P302 Part A:** 43 (39.1) **P302 Part B:** 106 (51.5)			
Unsolicited AEs	Related AEs, up to 28 days after injection (any grade)	n (%)	**P303 Part A:** 17 (1.7) **P101:** 6 (10.2) **P101 WOCBP:** 5 (3.4) **P302 Part A:** 1 (0.9) **P302 Part B:** 1 (0.5)		**SoE:** Consistently low related unsolicited AE rates outside small subgroups. **Unc:** Causality assignment is inherently variable; small N in P101 inflates percentages.	P101; P302 Part A & B; P303
AESIs	Regardless of relationship, up to EoS/DCO	n (%)	**P303 Part A:** 2 (0.2) **P101:** 0 **P101 WOCBP:** 1 (0.7) **P302 Part A:** 0 **P302 Part B:** 2 (1.0)		**SoE:** Longer follow-up context (EoS for P101/P302; DCO for P303). **Unc:** Very rare AESIs cannot be excluded.	P101; P302 Part A & B; P303

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; CI=confidence interval; DCO=data cut-off; GMT=geometric mean titre; GMR=geometric mean ratio; NI=non-inferiority; SR=seroresponse; SRR=seroresponse rate; yoa=years of age.

Notes: No safety data for the control population (≥60 years) were included in this variation.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The key favourable effect supporting the proposed extension of indication is the demonstration of a statistically robust and methodologically sound immune response in adults aged 18 to <60 years that is non-inferior to that observed in older adults in whom clinical efficacy has been established. No immunogenicity data were generated in healthy individuals 18-59 years of age, but all immunogenicity data in this age group are derived from individuals with chronic conditions associated with higher risk of RSV-associated LRTD. However, this immunobridging approach provides a scientifically acceptable basis to infer clinical benefit in the younger adult population and is supported by the consistency of responses across relevant subgroups and the observed persistence of antibody responses.

The unfavourable effects identified to date are of low to moderate clinical importance. Reactogenicity was transient, predominantly mild to moderate and consistent with expectations for an mRNA-based vaccine, and is unlikely to meaningfully impact clinical decision-making. No safety signals of concern were identified for adverse events of special interest, albeit differences in reactogenicity observation windows across studies (notably P302 vs P303/P101) may limit comparability and could underestimate reactogenicity in P302; clarifications of the diary window were therefore provided. However, residual uncertainties remain regarding the potential for very rare adverse events and the characterisation of long-term safety in younger adults, as the available safety database is not powered to detect uncommon risks and long-term follow-up is currently limited. In addition, missing information on use during pregnancy is a relevant unfavourable consideration in the context of the expanded indication. Overall, the importance of the unfavourable effects is driven primarily by remaining uncertainties rather than by identified safety risks and these uncertainties are considered clinically relevant but manageable through ongoing and planned post-authorisation safety activities.

3.7.2. Balance of benefits and risks

Considering the relative importance of the identified effects, the benefit-risk balance for the proposed extension of indication to adults aged ≥18 years is driven by the overall consistency between a biologically plausible benefit and a safety profile without identified major concerns. The demonstrated immunogenicity in younger adults, shown to be comparable to that in an older population with established clinical benefit, provides a credible basis for benefit extrapolation, despite the absence of direct clinical efficacy data in the expanded population. However, the clinical benefit is less directly supported (and therefore less certain) in healthy adults aged 18 to 59 years than in older adults or in adults with conditions associated with an increased risk of severe RSV-LRTD.

The safety profile does not indicate a need for a direct trade-off between meaningful benefit and clinically significant harm. Observed adverse reactions are largely predictable and manageable and no signals have emerged that would outweigh the inferred benefit of vaccination in the target population. The main challenges in the benefit-risk evaluation relate to residual uncertainties, including the limited ability to characterise very rare adverse events and the currently incomplete long-term safety data in younger adults.

These uncertainties are considered acceptable in the context of a preventive intervention for a potentially serious respiratory infection, particularly given the ongoing and planned measures to further characterise safety post authorisation. On balance and based on the available evidence, the CHMP is of the opinion that the benefits of extending the indication are considered to outweigh the identified and potential risks, provided that continued safety monitoring and appropriate risk communication are maintained.

3.8. Conclusions

The overall B/R of mRESVIA (mRNA-1345) for the proposed extension of indication to adults aged ≥18 years 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(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

Extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in all adults 18 years of age and older for mRESVIA, based on results from Study mRNA-1345-P101, Study mRNA-1345-P301, Study mRNA-1345-P303 Part A, and Study mRNA-1345-P302 Part A and Part B. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted.

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, IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000312911