EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2024
EMA/329706/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

mResvia

International non-proprietary name: Single-stranded 5' capped mRNA encoding the respiratory syncytial virus glycoprotein F stabilised in the prefusion conformation

Procedure No. EMEA/H/C/006278/0000

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
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ATP	adenosine triphosphate
BSA	bovine serum albumin
CFU	colony-forming unit
CM	critical material
CMA	critical material attributes
CoA	certificate of analysis
CPP	critical process parameter
CQA	critical quality attribute
CTP	cytidine triphosphate
CTU	controlled-temperature unit
DNA	deoxyribonucleic acid
DP	drug product
DS	drug substance
dsRNA	double-stranded RNA
dT	deoxythymidine
EDTA	ethylenediaminetetraacetic acid
GMP	good manufacturing practice
GTP	guanosine triphosphate
HPLC	high performance liquid chromatographic separation
IPC	in-process control
IVT	*in vitro* transcription
kDa	kilodalton
LDP	labelled drug product
LNP	lipid nanoparticle
LRR	leachable risk rating
MCB	master cell bank
mRNA	messenger ribonucleic acid
MWCO	molecular weight cut-off
NGS	next generation sequencing
NWP	normalised water permeability
ORF	open reading frame
PAR	proven acceptable ranges
PP	process parameter
PPQ	process performance qualification
qPCR	quantitative polymerase chain reaction
SAM	s-adenosylmethionine
SUM	single-use mixer

TFF	tangential flow filtration
TMP	transmembrane pressure
UDP	unlabeled drug product
UTR	untranslated region
WCB	working cell bank
WFI	water for injection
WRM	working reference materials

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Moderna Biotech Spain S.L. submitted on 26 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for mResvia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

> Active immunisation for the prevention of lower respiratory tract disease (LRTD) and acute respiratory disease (ARD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0195/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0195/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.4.2. Derogations from market exclusivity

Not applicable.

1.5. Applicant's request for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance Single-stranded 5' capped mRNA encoding the respiratory syncytial virus glycoprotein F stabilised in the prefusion conformation contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Not applicable

1.7. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
16 September 2021	EMA/SA/0000063940	*Mair Powell and Ingrid Schellens*
26 April 2023	EMA/SA/0000130430	*Jens Reinhardt and Dieter Deforce*

The scientific advice with case number EMA/SA/0000063940 pertained to the following clinical aspects:

- Dose selection;
- Phase 2/3 study design including study population, duration, endpoints and statistical plan.

The scientific advice with case number EMA/SA/0000130430 pertained to the following quality aspects:

- Acceptability of the manufacturing process validation of the RSV vaccine; comparability strategy for RNA, LNP and finished product; mRNA analytical method validation strategy; release tests to be included in the potency testing; approach for the determination of initial shelf life; proposed strategy to demonstrate comparability between mRNA used in clinical trials and that intended for commercial supply.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	26 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to mResvia on	27 June 2024

During the assessment of the application for the marketing authorisation of mResvia, the following non-EU authorities were allowed to participate as part of the OPEN framework and contribute to the scientific discussions of the CHMP: Swissmedic. This authority did not participate in the overall benefit/risk determination, which was decided by the CHMP.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Respiratory syncytial virus (RSV) is a ribonucleic acid (RNA) virus belonging to the genus Orthopneumovirus within the family Pneumoviridae of which 2 antigenically distinct subtypes exist, RSV-A and RSV-B.

RSV has been identified as one of the important aetiologies of acute respiratory infection (ARI) in older adults and is increasingly recognised as a major cause of illness in all high-risk adults, including those with chronic lung and heart disease (Falsey et al 2005, Shi et al 2020). The overwhelming majority of RSV mortality in industrialised countries occurs in those that are above 65 years of age (Korsten et al 2021). RSV is transmitted primarily via aerosolised droplets from the sneeze, cough, or breath of an infected person, or via contamination of environmental surfaces with infectious secretions. Upper respiratory symptoms typically begin within several days of RSV infection. The virus may descend to the lower respiratory tract, leading to wheezing, bronchiolitis and potentially hospitalisation, respiratory failure, mechanical ventilation, and even death. Infections with RSV follow a seasonal pattern, typically occurring in the Northern hemisphere between the months of November and April, and in the Southern hemisphere between March and October.

2.1.2. Epidemiology

RSV causes annual epidemics, generally during the winter season in temperate climates and during the rainy season in tropical regions. However, year-round circulation of RSV activity can occur. Two prospective cohort studies estimated the incidence of RSV infection in older adults: one in the UK from 1992 to 1994 showed an incidence of 36 per 1000 person-years and another across several European countries from 2017 to 2019 recorded an incidence rate of 4.2% to 7.2%, as determined through both PCR and serology tests. Using 2019 census data from Europe, RSV was estimated to have caused 3.0 million acute respiratory infections, 274,000 hospitalisations, and 20,000 in-hospital deaths in 2019. Studies conducted in the United States and Japan indicate that RSV may contribute to between 3% and 15% of community-acquired pneumonia, 9% to 10% of hospital admissions for acute cardiorespiratory diseases, and approximately 6500 excessive deaths during seasonal peaks in older adults. RSV hospitalisation incidence has been found to increase with age, with noteworthy variations reported across different racial and ethnic groups. Indigenous populations, attributed to inadequate healthcare access, household crowding, and high indoor smoke levels, experience higher burdens of RSV disease. Additionally, risk factors include advanced age, comorbidities and frailty. The disease manifests variably in older adults, from mild cold symptoms to severe respiratory distress, and cough and fever are common. The COVID-19 pandemic altered the timing and magnitude of usual RSV seasonality across the globe. In the US, following the COVID-19 pandemic, the reported peak rate of RSV hospitalisation in older adults increased approximately 2-fold and occurred 2 months earlier than in the pre-COVID-19 pandemic years, 2017/2018 and 2019/2020. Modelling data suggest that following the COVID-19 pandemic, the seasonality of RSV will remain atypical, after which the viruses will likely return to their expected seasonality.

2.1.3. Clinical presentation, diagnosis

Symptomatic RSV usually starts as an upper respiratory tract infection, that can lead to more serious disease by involving the lower respiratory tract.

The most common symptoms include nasal congestion/rhinorrhoea, sore throat, cough, sputum, dyspnoea, wheezing, rhonchi, shortness of breath, and decreased oxygen saturation. In addition, systemic signs include fever, fatigue, body aches, headache and decreased appetite.

2.1.4. Management

Treatment

An antiviral agent, ribavirin, is licensed for the treatment of RSV infection in the United States and some EU member states. This drug is not recommended in the EU guidelines.

Prevention

At the time of review of the MAA, there were two licensed vaccines for the prevention of RSV-associated diseases in adults ≥60 YoA.

2.2. About the product

The applicant's candidate respiratory syncytial virus (RSV) vaccine consists of 50 µg RNA-100-AR02 encoding the respiratory syncytial virus (RSV) F glycoprotein stabilised in the pre-fusion conformation.

At the time of submission, the claimed therapeutic indication was:

Active immunisation for the prevention of lower respiratory tract disease (LRTD) and acute respiratory disease (ARD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.

The recommended dosing regimen for RSV vaccine Moderna is a single dose of 0.5 ml.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as it was considered that there was no unmet medical need. The applicant did not provide any evidence of any therapeutic advantages compared to other approved products.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as single dose prefilled syringe containing 50 micrograms per 0.5 ml dose of respiratory syncytial virus (RSV) mRNA vaccine (nucleoside modified) as active substance.

The active substance is a single-stranded 5' capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion conformation. It is encapsulated in lipid nanoparticles.

Other ingredients are: SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, water for injections.

The product is available in in a pre-filled syringe (polymeric barrel) with plunger stopper and a rubber tip cap (without needle).

2.4.2. Active Substance

2.4.2.1. General Information

The active substance RNA-100-AR02 (internal name CX-032753), encodes for the respiratory syncytial virus (RSV) F glycoprotein stabilised in the pre-fusion conformation. The molecular sequence of RNA-100-AR02, including the 5′ cap, the 5′ untranslated region (UTR), the Open Reading Frame (ORF), the 3′ UTR, and the 3′ polyA tail, is provided in the dossier.

2.4.2.2. Manufacture, process controls and characterisation

RNA-100-AR02 is manufactured and tested at the site ModernaTX, Inc. (ModernaTX Norwood) One Moderna Way Norwood, MA 02062 USA. The GMP compliance of the manufacturing and testing sites has been confirmed.

Description of manufacturing process and process controls

The manufacturing process of RNA-100-AR02 has been adequately described. The main steps comprise of an *in vitro* transcription (IVT) where uncapped RNA is synthesised enzymatically using a linearised plasmid template to produce the desired full-length RNA with a polyadenylated (PolyA)) tail. Tangential flow filtration (TFF) is performed to exchange buffer and concentrate the RNA prior to loading of the chromatography column. The RNA is captured by chromatography, washed to reduce process-related impurities, and eluted. A second TFF is performed to adjust RNA concentration, followed by an enzymatic Cap Reaction to produce Cap1 modified RNA. A third TFF is performed for buffer exchange and to adjust RNA concentration for the second chromatography step to capture the RNA and remove process-related impurities from the Cap Reaction. A Final TFF is performed to concentrate the RNA and for buffer exchange into Final Storage Buffer, followed by a bioburden reduction clarification step. The resulting RNA is dispensed for storage at -25°C to -15°C or -90°C to -60°C.

The individual process steps are controlled with numerous process parameters. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. The manufacturing of the MCB and WCB of the plasmid as well as the release testing and the qualification protocol of new MCB/WCB are described conclusively. The linearised plasmid that is considered as the starting material is thoroughly tested. The applicant also provided a conclusive description of the raw materials used. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. CoAs were provided within the submission package.

Control of critical steps and intermediates

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale PPQ batches. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

During the procedure a major objection (MO) was raised as the proposed process characterisation and control strategy relied on platform data including data from non-licensed products. In response, the applicant provided product specific documents regarding process development and validation. The process validation is now product-specific clearly indicating if supportive data from the approved product, Spikevax, was used. The validated IVT reaction volume is defined.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme and the process development is described in detail. It is appreciated that certain aspects especially from the licensed vaccine Spikevax are used to support the process development of RNA-100-AR02. A table is provided indicating the differences between the Spikevax and RNA-100-AR02 commercial processes, with justifications if changes were implemented. Scale-down models to determine critical process parameters and establish PARs were conducted with the actual applied product and justified the proposed critical process parameters and PARs.

Concerning the residual DNA and protein, residual DNA is now included in the release testing panel. The resin lifetime studies are considered acceptable.

The comparability exercise to justify the switch from RNA-100-AR01 to RNA-100-AR02 after clinical development is considered acceptable.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure. The applicant provided a detailed package of characterisation studies to elucidate the structure and the impurities of mRNA-1345. The analytical results are consistent with the proposed structure.

For high molecular weight impurities, the applicant showed that these product-related variants do not affect the protein expression. Furthermore, no induction of immune stimulation by uncapped mRNA can be seen due to usage of a proprietary T7 polymerase version, and potentially stimulatory dsRNA is consistently low throughout the process scale-ups. For residual plasmid DNA a more sensitive fragmentation assay should be developed to characterise the actual fragmentation of the residual plasmid DNA template to determine the efficacy of the DNase treatment and the following purification process.

RNA is stored frozen in a gamma irradiated, single-use storage bag as a low-bioburden material. The description and testing of the container closure system is considered acceptable. The simulated leachable study report and the equivalency assessment report used to ensure that the findings of the simulated leachable study performed for mRNA-1273 RNA are applicable to RNA-100-AR02 were provided.

2.4.2.3. Specification

Specification

The active substance specification includes tests for appearance, identity (reverse transcription/Sanger sequencing)-, Total RNA content (UV), mRNA purity (RP-IP-HPLC), product related impurities (RP-IP-HPLC), % Cap1 (RP-IP-HPLC), % PolyA tailed RNA (RP-HPLC), % tailless RNA (RP-HPLC), residual DNA template (qPCR), pH (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and bioburden (Ph. Eur.).

The justification of the specifications and acceptance criteria are considered acceptable.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. As a platform analytical approach is selected only sequence/product-specific methods are re-validated, whereas the other methods are already validated due to their use for Spikevax. This approach is considered acceptable. However, as the documentation is not very clearly structured the applicant was asked to adapt the table in the dossier clearly indicating which method at which site was re-validated using mRNA-1345 material.

Batch analysis

Batch analysis data (from the PPQ lots) of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The description of the reference standard is considered acceptable and also details how future reference material will be qualified are included. The reference standard for the commercial production is derived from a registration lot. It was thoroughly tested and characterised and will be followed up by a stability monitoring protocol.

2.4.2.4. Stability

Three registration batches of active substance were placed on stability at long term, interim and accelerated storage conditions.

In response to questions raised, updated real-time, real-condition stability data were provided for the PPQ lots and supportive data for development batches. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container. The proposed shelf-life claim and storage condition is considered acceptable.

It was noted that the final stability report will be provided as soon as the stability study is completed.

2.4.3. Finished Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is composed of mRNA-1345 lipid nanoparticles formulated with tris buffer, acetate and sucrose at pH 7.5. The finished product contains 0.1 mg/ml RNA-100-AR02 which equates to 50 µg RNA per 0.5 ml dose.

The excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards and/or in-house specifications, where applicable. There are no novel excipients used in the finished product formulation.

The SM-102 and PEG2000-DMG lipid excipients are proprietary excipients. These excipients are previously authorised in the Spikevax COVID-19 vaccine, MAH: Moderna.

SM-102 is the ionizable lipid component of the lipid mixture (LMX). Under the acidic conditions of the encapsulation reaction, the net positive charge of SM-102 drives the spontaneous encapsulation of the negatively charged RNA through electrostatic attraction.

The PEG2000-DMG lipid enhances colloidal stability of the LNP dispersion but also reduces cell uptake. The lipid portion of the PEG-lipid anchors itself into the lipid layer of the LNP while the PEG provides steric stability.

The primary packaging of the finished product is single-dose 1-ml cyclic olefin copolymer (COC) syringe. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. During the procedure, a MO was raised as a notified body opinion for the pre-filled syringe (PFS), pursuant to General Safety and Performance Requirements in Annex I of Regulation (EU) 2017/745, had not been provided in the initial submission. In response, the relevant notified body opinion for the prefilled syringe was provided and the MO was considered to be resolved.

Developmental stability studies have been performed. Photostability studies support the finished product manufacturing under normal room lighting conditions although the finished product is sensitive to UV-A and visible light. A transport simulation study demonstrates that the vaccine can be transported in a frozen or liquid state (at -25°C to -15°C or at 2°C to 8°C).

The development of the manufacturing process from first-generation to second-generation to third generation to the commercial process has been sufficiently described.

A first-generation finished product lot with different buffer composition and lyophilised presentation has been used in the dose escalation study P101. In the pivotal phase 3 study P301, a second-generation batch and a third-generation batch have been used. Lots manufactured according to the second and third generation process had similar buffer composition as the commercial formulation, but the finished product concentration in the second-generation process is higher. There are only minor changes between third generation and commercial process, mainly consisting of a process upscale with different mixing vessel and a change of the container closure system from vial to prefilled syringe. Within the third-generation process, the mRNA sequence has been changed. However, the differences in the RNA sequence are minor and only concern the UTR region (see discussion in active substance part). Comparable protein expression from finished product containing the different RNAs has been shown. Therefore, it is acceptable that the further comparability assessment between clinical and commercial (registration) lots is limited to release testing results. Release testing results are in good agreement between clinical and commercial lots and also comparable to developmental lots.

Leachables and extractables of the process consumables have been addressed. It is agreed that the leachables/extractables studies done for Spikevax are also representative for the current application, because the concentration and composition of the LNPs is the same and the process is the same and uses the same equipment.

2.4.3.2. Manufacture of the product and process controls

The GMP compliance of all manufacturing sites has been confirmed.

The finished product manufacturing process has been described and includes the manufacture of mRNA-1345 LNP Intermediate and mRNA-1345 Finished Product.

2.4.3.3. mRNA-1345 LNP Intermediate

The mRNA-1345 LNP intermediate consists mainly of a mixture of four lipids, SM-102, cholesterol, DSPC and PEG2000-DMG (referred to as LMX-100) and the mRNA (RNA-100-AR02) that encodes for the RSV F glycoprotein stabilised in the prefusion conformation.

For the process qualification, a sufficient number of registration lots per manufacturing site were manufactured and extensively characterised so that these can be considered as PPQ lots. Overall, the process validation and its scope are considered sufficient.

The mRNA-1345-LNP manufacturing process aims to encapsulate RNA into the lipid mixture. In principle, this process consists of mixing the ingredients, followed by neutralisation, clarification and filling. The processes are identical at all manufacturing sites, only the size of the final storage bags differs.

During development, various manufacturing processes were used. These are referred to as 1st, 2nd and 3rd generation. Phase 3 clinical trials were conducted using material from the 2nd generation manufacturing process only. For the comparability analyses, clinical lots produced with the 2nd generation manufacturing process including additional clinical lots from development and commercial lots were compared. The results show that the process is consistent across the different manufacturing sites. Higher lipid impurities tend to be detected at one manufacturing site, which should be further investigated post-approval. It is also recommended to repeat the in-process hold time qualification study with a representative sample processing without additional freezing and thawing step post-approval.

In general, the specifications proposed for the mRNA-1345 LNP intermediate are considered sufficient; however, there were initially several concerns regarding the proposed acceptance criteria, with only a small number of clinical lots available to sufficiently justify the limits clinically. In response the applicant adapted the specifications for some specification attributes. In contrast, no adjustment was made to other specification attributes as the proposed specification supports further processing to the finished product, which is deemed acceptable. The specification for the particle size is proposed to be tightened. The applicant states that this adjustment is based on statistical calculations considering product shelf life, further processing and the evaluation of process and analytical compatibility. It is therefore expected that the applicant will further tighten the LNP particle size specification after gathering additional batch data using a 2-sigma limit (REC 5).

The analytical procedures are adequately described and validated, and impurities are sufficiently characterised. RNA from the active substance manufacturing process is used as reference material for the purity assays of the mRNA-LNP intermediate, as well as for the determination of the RNA content. The use of pure RNA as reference material is justified by the applicant and is deemed acceptable.

The container closure system used for the mRNA-1345-LNP intermediate is single-use storage bags, which is considered well characterised and controlled.

The proposed shelf-life of the mRNA-1345-LNP intermediate when stored in the commercial container closure system at the recommended storage condition was defined. Limited stability data were available at the time of initial submission and the shelf-life claim was mainly based on statistical data from development batches.

2.4.3.4. mRNA-1345 Finished Product

The batch formula has been provided for a batch size range of finished product.

The manufacturing process has been sufficiently described in the dossier. The main steps are: mRNA-LNP thawing and pooling, dilution with dilution buffer, clarification filtration, sterile filtration, aseptic filling, visual inspection, labelling/packaging and long-term storage at -50°C to -15°C after conditioning freeze. Two alternative flows are included: Flow 1 with an intermediate storage step of the UDP of up to 3 months including freeze/thaw before labelling/packaging and Flow 2 for continuous processing leading directly to the final drug product (labelled drug product LDP). In-process controls and process parameters are adequately chosen.

During the procedure a MO has been raised because the applicant has defined a process named "UDP-100-AR02 Drug Product Manufacturing Process" that only covers the process up to the unlabelled drug product (UDP). Since UDP is not only unlabelled, but a freeze/thaw step and a storage time is included before the final finished product (labelled drug product, LDP) is manufactured, it was not acceptable that comparability, process validation, release testing and stability only covers the process up to UDP. In response, the applicant has renamed the process and provided the relevant data for the whole process up to LDP, and the MO is considered to be resolved. The manufacturing process development now characterises the process/product until the LDP stage.

During the procedure several issues had been raised regarding process characterisation. In response the applicant updated the dossier to replace previously included platform data by product-specific data. The selection of CPPs and CIPCs has been described and is principally supported. Suitable critical process parameters have been defined and are adequately controlled. Adequate critical in-process controls have been established. A suitable microbial control strategy has been chosen that includes appropriate manufacturing areas, microbial control testing and media fills.

Process validation has been performed with consecutive batches at commercial scale and covers the whole batch size range. The process validation approach is in principle adequate and the results of release testing, critical and non-critical IPCs and critical and non-critical PPs confirm that the process is consistently producing final medicinal product of the expected quality.

The microbiological quality attributes are sufficiently controlled during the manufacturing process and at release. The proposed cumulative process duration (CPD) challenged with some samples during PPQ and supports the total processing time.

2.4.3.5. Product specification

The finished product specification includes tests for appearance, identity (reverse transcription/Sanger sequencing), total RNA content (AEX-HPLC), mRNA purity (RP-IP-HPLC), product related impurities (RP-IP-HPLC), %RNA encapsulation (absorbance), particle size (DLS), polydispersity (DLS), cell free translation (wheat germ cell free translation (CFT) system), in vitro relative protein expression (ELISA), lipid identity (HPLC-CAD), lipid content (HPLC-CAD), lipid-related impurities (HPLC-CAD), particulate matter (USP), deliverable volume (Ph. Eur.), break loose force / glide force, pH (Ph. Eur.), osmolality (Ph. Eur.), bacterial endotoxins (Ph. Eur.), container closure integrity and sterility (Ph. Eur.).

As a response to the initially raised MO3, all batch release testing except for sterility and bacterial endotoxin is now performed on LDP.

During the procedure an MO was raised as the initial appearance acceptance criterion allowed the presence of "[…] visible, white or translucent product-related particulates" for both the DP Intermediates and the Final Product, even though such particulates have not been observed to date. In response the applicant updated the appearance acceptance criterion to "White to off-white dispersion. Essentially Free from Visible Particulates".

A cell-based assay has been included in the release testing. However the EOSL specification proposed was not considered clinically justified and was changed after an additional MO was raised. The decrease rates at different temperatures should be re-calculated when more stability data is available (REC 7). Furthermore, the applicant was asked to re-examine the %RPE release specification after a substantial number (for example 20) of commercial batches have been produced (REC 6).

The RNA purity by PR-IP-HPLC assay is another important stability-indicating test. The initially proposed specifications at the end of shelf life (EOSL) have not been sufficiently justified by clinical data. Further justification has been requested as an MO. In addition, the lower limit for %RNA encapsulation has to be taken into account because all clinical batches had consistent RNA encapsulation rates. In response the EOSL specification for RNA purity in finished product has been adapted. All methods relevant for finished are sufficiently described or reference to Ph. Eur. is made. However, only the identity test has been validated using mRNA-1345 finished product. For the other tests, the applicant has committed to perform method validation (RNA purity test) or method verification, but data is not yet available. Results of the RNA purity test method transfer and of the method verifications site should be provided (REC 4).

Batch analysis results are provided for commercial finished product (PPQ UDP) lots and show consistent results. Supportive batch data for PPQ LDP lots, which will not be commercially used, have also been provided and show consistent results.

No new product-related or process-related impurities occur during formulation of the final finished product. Impurities are thus addressed on the active substance and intermediated DP level. Relevant impurities are also part of the batch release testing.

The applicant has provided a risk assessment for the presence of nitrosamine impurities in the final vaccines. The main risk for introduction of nitrosamine impurities has been identified by lipids used for nanoparticle formation. In response to questions, the nitrosamine risk assessment was updated to also cover the equipment and container closure system. The applicant’s conclusion that results show a negligible risk for the presence of nitrosamines is supported.

Components of the container closure system are sufficiently described and are compliant with the relevant requirements. Leachables and extractables of the process consumables have been addressed. It is agreed that the leachables/extractables studies done for Spikevax are also representative for the current application, because the concentration and composition of the LNPs is the same and the process is the same and uses the same equipment.

2.4.3.6. Stability of the product

The available real time stability data from PPQ lots includes results up to 12 months stored at -20°C and 2-8°C for one PPQ LDP lot, and up to 6 months at -20°C and 2-8°C for the other PPQ LDP lots. This data is most relevant for the shelf-life claim. Stability data is also available from clinical lots, but the RNA concentration or container closure system differ from the commercial lots.

During the procedure, MOs were raised on the finished product stability as the initially proposed shelf life for the finished product was not supported, and applicant’s first alternative proposal, was also not suitable. In their final response, the applicant proposed a shelf of 12 months at -40°C to -15°C including up to 1 month of storage at 2°C to 8°C and up to 24 hours at room temperature was proposed. Based on the provided stability data, a total the shelf life of 12 months is supported. The time at 2-8°C is determined by the decrease of the CQAs purity and %RPE. In addition to the real-time data, the stability of the RSV vaccine is statistically modelled to predict the decrease in RNA purity and %RPE over time dependent on the storage temperature. The predicted RNA degradation rates and

%RPE decrease rates are given for the temperature ranges -25°C to -15°C, 2-8°C and 23-27°C. This approach is principally supported and questions regarding the appropriateness of the statistical approach have been answered. Given the agreed release and EOSL values for %RPE and RNA purity, storage for 1 month at 2-8°C is justified. Furthermore, the applicant commits to provide the IVRPE data from an additional stability study by March 2026 (REC 8).

In conclusion, the finished product shelf life of 12 months stored at -20°C, including up to 1 month at 2-8°C and 24 hours at 15°C to 25°C, is considered to be acceptable. The proposed "In-Use Time" of at least 12 hours at room temperature for the vaccine is sufficiently justified.

2.4.3.7. Post approval change management protocol(s)

Not applicable.

2.4.3.8. Adventitious agents

Adventitious agents' safety for RNA-100-AR02 active substance, mRNA-1345 LNP intermediate, and mRNA-1345 DP finished product is assured through the design and control of the manufacturing process, i.e., controlled selection and appropriate specifications for raw materials and consumables, in-process controls, and release testing for the active substance and the finished product.

2.4.3.9. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure a number of major objections were raised on quality aspects (i.e. active substance process characterisation and control strategy, finished product manufacturing process, finished product specifications, finished product stability data, notified body opinion for the prefilled syringe). The applicant has responded to these by providing the requested information and has updated their dossier accordingly. Therefore, as discussed in detail in the preceding sections, these were considered to be satisfactorily resolved.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues that have no impact on the Benefit/Risk ratio of the product, which pertain to commitments from the applicant to provide various additional confirmatory data and to re-examine certain quality attributes when further commercial manufacturing experience is gained. These points are agreed as recommendations for future quality development listed under section 2.4.6.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product, mResvia, is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant commits to generate data to characterise fragmentation of the residual plasmid DNA template to demonstrate the efficacy of the DNase treatment and the following purification process by Q2 2025.
2. The applicant commits to monitor the levels of lipid impurities and provide the results of 10 batches from each manufacturing site. Based on the current manufacturing schedule, the applicant anticipates providing the comparative results by 2027.
3. The applicant commits to perform the in-process hold time qualification study with representative sampling handling without the additional freeze-thaw step by 31 December 2024.
4. The applicant commits to provide the requested method validation data within 1 month of the EC decision by October 2024.
5. The applicant commits to re-examine the mRNA-1345 LNP particle size specification after the production of 20 further batches based on an appropriate statistical analysis. Based on the current manufacturing schedule, the applicant anticipates providing the comparative results by the end of 2027.
6. The applicant commits to re-examine the %RPE finished product release specification after the production of at least 20 further commercial batches. Based on the current manufacturing schedule, the applicant anticipates providing the comparative results by the end of 2025.
7. The applicant commits to re-calculate the %RPE decrease rates at -20°C, 2-8°C and 25°C after additional finished product stability data is available, and to adjust the shelf life conditions if appropriate. The applicant anticipates providing updated stability analysis with additional mRNA-1345 finished product lots by the end of 2027.
8. The applicant commits to provide the IVRPE data from the additional study by March 2026.

2.5. Non-clinical aspects

2.5.1. Pharmacology

mRNA-1345 consists of mRNA encoding the RSV F protein stabilised in the prefusion conformation formulated in an LNP dispersion composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG. The same SM-102-containing LNP matrix is also present in Moderna's Spikevax Covid-19 vaccine.

A few non-GLP-compliant non-clinical pharmacology studies were conducted in mice and cotton rats to characterise the immunological properties of mRNA-1345.

In an *in vivo* dose-response study (Report 3823-1), female BALB/c mice, 6 to 8 weeks of age, were intramuscular (IM) administered mRNA-1345 at 0.1, 0.2, 1, and 5 µg in 2 different presentations (liquid and lyophilised) on Days 1 and 22. Two IM injections induced high levels of binding and neutralising antibodies consisting of a balanced IgG2a:IgG1 response, indicating a Th1 response.

A separate mouse study (Report X-107 Amendment 1) was performed to evaluate the immunogenicity of mRNA-1345 at 5 µg dose level administered IM on Days 0, 21, and 49. Results were compared to

the formalin-inactivated respiratory syncytial virus vaccine (FI-RSV) and to the recombinant prefusion F protein (preF) adjuvanted with Alhydrogel. mRNA-1345 induced a robust RSV neutralising and binding antibody response. The RSV antibody response induced by mRNA-1345 was largely functional, i.e. neutralising antibody. In contrast, the antibody response induced by FI-RSV was primarily non-functional (i.e. non-neutralising) and directed to the post-fusion F protein (postF) conformation. This study further revealed that vaccinations with 3 IM doses of mRNA-1345 at fixed 5 µg dose could elicit type 1 cytokine-producing CD4+ and CD8+ T-cell responses and a balanced IgG2a:IgG1 antibody response. In contrast, FI-RSV and recombinant preF adjuvanted with Alhydrogel-induced Th2 responses, as indicated by type 2 cytokine-producing CD4+ T-cells, no CD8+ T-cells, and an IgG1-biased antibody response. These data indicate that mRNA-1345 induced an immunologic profile characteristic of protection that was distinct from the disease-enhancing phenotype induced by FI-RSV.

In an *in vivo* efficacy study (Report XV-224 Amendment 1), the immunogenicity of mRNA-1345 was evaluated in female cotton rats at dose levels of 0.0003, 0.003, 0.03, 0.3, 3, and 30 µg administered IM on a prime (Day 0) or a prime/boost schedule (Days 0 and 28). Results were compared to FI-RSV and live RSV (A2 virus, intranasal) controls. Additionally, the potential for RSV vaccine-associated enhanced respiratory disease (VAERD) was appropriately evaluated. Data indicated a dose-dependent immunogenicity and protective effect of mRNA-1345 vaccine after 2 IM injections. A 2-doses series of mRNA-1345 at doses ≥ 0.3 µg induced comparable or higher titres of neutralising antibodies, relative to live RSV virus infection (10^5 PFU). Interestingly, a single IM dose of mRNA-1345 at 0.3 µg was still found to be immunogenic in this model and to confer partial protection of the lung from RSV challenge. Nevertheless, the antibody response at day 56 post vaccination was significantly stronger in the two-dose group compared to the one-dose group. There seems to be a good correlation of serum RSV neutralising titres with protection of the lung RSV infection in mRNA-1345 vaccinated animals, however, correlation with protection against nose infection was very weak. Whether T-cell immunity or local mucosal immunity play a role in full protection, especially in protection against nose infection in group of animals receiving 30 µg of mRNA-1345, cannot be determined. The immunological and histological data from this study demonstrated that mRNA-1345 induced antibody response was largely functional and preF-biased, without promoting enhanced lung inflammation or induced Th2 cytokines after RSV challenge. This is in contrast to the immunopathological data obtained from FI-RSV-vaccinated animals, showing an antibody response primarily non-functional and directly to postF conformation, and enhanced lung inflammation and Th2 cytokines after RSV challenge. Together, the study in the cotton rat model provides important rationale for use of mRNA-1345 in human adults.

Another study in female BALB/c mice to compare mRNA-1345 containing either RNA-100-AR01 or RNA-100-AR02 revealed no impact on the vaccine-induced IgG response.

No secondary pharmacodynamics studies, stand-alone safety pharmacology studies, and pharmacodynamics drug interaction studies were conducted with mRNA-1345, which is in line with the regulatory guidelines and thus acceptable.

Overall, the pharmacological testing of mRNA-1345 candidate vaccine is adequate, with no major objection being raised from nonclinical pharmacology aspect. In the applicant submitted Day 120 responses, it was clarified that, animals in studies 3823-1, X-107 amendment 1, and XV-224 amendment 1 were 6-8 weeks of age with a naïve pre-dose immunological status, they had no prior exposure to RSV or mRNA-1345. In addition, the microneutralisation assay employed in these studies was a research-grade assay that was not qualified or validated.

2.5.2. Pharmacokinetics

No pharmacokinetic (PK) studies have been conducted with mRNA-1345. A biodistribution study performed was conducted in male Sprague Dawley rats with mRNA-1647 (Report 5002121 Amendment

2), a mRNA-based CMV vaccine that was formulated in the same SM-102-containing LNP matrix. The same study was previously used to support the development of Moderna's Spikevax (mRNA-1273). The data from this biodistribution study performed with mRNA-1647 indicated that mRNA construct could be distributed to most tissues analysed except for kidney, after single IM administration. The highest mRNA concentrations were observed at the injection site (muscle), followed by the proximal (popliteal) and distal (axillary) lymph nodes, suggesting distribution via the lymphatic system. Overall, only a relatively small fraction of the mRNAs in mRNA-1647 drug product distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site (muscle), lymph nodes, and the spleen.

It is noted that, the ratio of PEG2000 component in LNP matrix included in mRNA-1345 differs from that in LNPs matrix included in mRNA-1647. In the applicant's Day 120 response, the applicant stated that a modest (2-fold) increase in PEG2000 within mRNA-1345 LNP matrix wouldn't be expected to result in different cleavage rate *in vivo* or different kinetics and distribution in systemic circulation and tissues. The GLP toxicology data from different toxicity studies showed consistency in the target organs and toxicological findings of mRNA vaccines formulated in an SM-102-containing LNP matrix with PEG2000-DMG:RNA ratios ranging from 1:1 to 2:1 and with different particle sizes.

The submitted nonclinical PK evaluations also included SM-102 lipid metabolism and excretion *in vivo* studies in Sprague Dawley rats and metabolite identification study *in vitro* (Report NCS-BA-2022-010). For these purposes, samples of plasma, urine and bile from male Sprague Dawley rats were obtained at different time points following a single 10-minute intravenous (IV) infusion administration of RNA formulated in an SM-102-containing LNP matrix (0.7 mg/kg). Samples for *in vitro* study were the cryopreserved primary hepatocytes, that were thawed, resuspended, and incubated with SM-102 at 10 µM concentration in 250 µL volume. Liquid chromatography (LC)-high resolution mass spectrometry (HRMS) was employed for identifying and qualitatively characterising metabolites of SM-102, whereas LC-MS/MS used for quantitation of the parent SM-102 in the *in vivo* samples. The SM-102 quantitation range was 0.2- 500 ng/mL with LLOQ – 0.2 ng/mL in rat urine; and 1- 500 ng/mL with LLOQ – 5 ng/mL in rat plasma and bile. The *in vivo* study showed rapid clearance of SM-102 and the elimination of SM-102 and its metabolites via the kidney (metabolites only) and liver (intact SM-102 and metabolites) to <3% of the maximum level by 24 hours after dosing. The metabolism of SM-102 in rats occurs primarily by hydrolysis of the ester groups followed by β-oxidation of the resulting aliphatic acidic linkers. Additionally, low abundance oxidative metabolites of ester-hydrolysed SM-102 fragments were detected. The *in vitro* incubation of SM-102-containing LNP matrix with rat, cynomolgus monkey, and human hepatocytes yielded identical ester-hydrolysed and β-oxidised metabolites with no human-specific metabolites detected. Based on the observed extensive metabolism of SM-102, the oxidative nature of the metabolites, and the multiple, ubiquitous, high-capacity systems by which they are formed, combined with the rapid overall clearance of SM-102 and elimination of its metabolites, it is reasonably assumed that SM-102 is unlikely to accumulate upon repeat IM dosing or be a risk for elimination in patients with hepatic or renal insufficiency.

Collectively, nonclinical PK data provide initial insight into the metabolism and excretion characteristics of SM-102 *in vivo*. However, caution may need to be exercised when interpreting these data, because analytic technique used in these studies was not validated. In the applicant's Day 120 response explained that use of IV route of administration was intended to maximise systemic exposure and ability to detect SM-102 parent and metabolites in plasma, bile, and urine, and that route of administration would not influence metabolism or elimination routes.

There were no PK drug interaction studies and other PK studies conducted with mRNA-1345, which is in line with regulatory guidelines and thus acceptable by the CHMP.

Overall, pharmacokinetics aspect of investigations submitted for mRNA-1345 candidate vaccine is considered **adequate** by the CHMP.

2.5.3. Toxicology

2.5.3.1. Single dose toxicity

No single-dose toxicity study with mRNA-1345 has been conducted. The local acute toxicity was analysed in several repeat-dose toxicity studies with mRNA-1345 or other mRNA platform vaccines. This approach is in line with relevant vaccine guidelines and considered acceptable.

2.5.3.2. Repeat dose toxicity

The company conducted a GLP-compliant repeat-dose toxicity study with mRNA-1345 and a non-GLP-compliant pilot toxicity study with mRNA-1345. In addition, GLP-compliant repeat-dose toxicity study data from the company's mRNA vaccine platform was submitted, using similar mRNA-based vaccines formulated in same SM-102 containing LNP matrix encoding for different antigens (ZIKV vaccines: mRNA-1706 and mRNA-1893, hMPV and PIV3 vaccine: mRNA-1653, and CMV vaccines: mRNA-1647 and mRNA-1443). These platform data were already submitted to support Spikevax marketing authorisation and were considered as adequate. Given the consistency of observed findings across the toxicity studies using different mRNA vaccines, the applicant concludes that the toxicities associated with mRNA vaccines formulated in LNPs are driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the consistency of the toxicological findings observed in these repeat-dose toxicity studies. It is noted that, the LNP composition in the different mRNA vaccines from the company's mRNA vaccine platform (mRNA-1706, mRNA-1893, mRNA-1653, mRNA-1647 and mRNA-1443) is slightly different to the LNP composition in the mRNA-1345 drug product; the concentration of PEG2000-DMG differs and thus, the ratio between the 4 lipids. According to the WHO guideline (WHO TRS No 1039, 2022, Annex 3), platform data can be acceptable when using mRNA vaccines with the same LNP composition than the LNP composition in the vaccine candidate for the intended marketing authorisation. Still, it is noted that, for the mRNA-1345 dossier, consistency in the target organs and toxicological findings was shown across different toxicity studies using mRNA vaccines that were formulated in an SM-102-containing LNP matrix with PEG2000-DMG:RNA ratios ranging from 1:1 to 2:1 and with different particle sizes.

Furthermore, different batches were used in the three non-clinical studies with mRNA-1345 (study 1021-9921, 2308-121 and 20312409). The applicant provided an adequate reassurance in the D120 applicant's responses to confirm that all the applied batches are representative for the final vaccine formulation used in the pivotal clinical studies.

It is endorsed that the Sprague Dawley rat was selected as the animal model for all conducted *in vivo* toxicity studies because it is a frequently used rodent species for nonclinical toxicology testing and is a relevant species to assess the toxicity and immunogenicity of mRNA vaccines, as evidenced by an immunogenic response (a robust antibody titre). In addition, historical control data are available as they are used routinely for regulatory toxicology studies.

In all repeat-dose toxicity, the IM route of administration was used because this is the intended route of administration in humans. The number of doses for the individual studies was 2 to 4 doses, and representative of the clinical plan (n+1) for each vaccine. A 2-week recovery period was selected in all platform repeat-dose toxicity studies with other mRNA vaccines based on previous studies in rats and was anticipated to demonstrate the reversibility of the findings. However, the GLP-compliant repeat-dose toxicity study with mRNA-1345 had no recovery period included, which is a major limitation of the

study design. This can be tolerated, because the observed findings for the mRNA-1345 toxicity studies were similar to the findings in the other platform vaccine toxicity studies. In the repeat-dose toxicity studies, the animals were assessed for clinical endpoints, ophthalmology examinations, clinical pathology parameters (haematology, coagulation, and clinical chemistry), post-mortem examinations (necropsy, (histo-)pathology), neutralising and/or binding antibodies and cytokine analysis (different interleukins, interferon gamma, acute-phase proteins). However, only in-life endpoints were assessed in the non-GLP compliant pilot toxicity study with mRNA-1345.

In the mRNA-1345 GLP-compliant repeat-dose toxicity study, a sufficient number of male and female rats were injected with two intramuscular doses of 98 µg/dose mRNA-1345, administered once every 3 weeks. However, a recovery group was not included in this study, which is a limitation of this study. Further, measurement of body temperature, urine analysis and species-appropriate acute phase reactants were not evaluated. No mRNA-1345-related mortalities were observed in this study. Both mRNA-1345 dose administrations were associated with oedema, erythema and limited use of the hindlimb and/or hindpaw. As observed for the first dose, these findings resolved within one week indicating recovery. In addition, lower mean body weight gain and food consumption was also observed, which resulted in a lower body weight in males only. mRNA-1345-related haematology changes consisted of mild increases in neutrophils and eosinophils, and mild to moderate decreases in lymphocytes, monocytes, reticulocyte and platelets in males and females at study termination. Furthermore, mRNA-1345-related coagulation changes consisted of mild increases in fibrinogen and minimal increase of activated partial thromboplastin time in males and females; and mRNA-1345-related clinical chemistry changes consisted of minimal increases in globulin, and mild decreases in albumin and albumin/globulin ratio in males and females. These vaccine-typical findings were consistent with inflammatory and immune system responses, respectively. However, samples for clinical pathology measurements were only collected at day 23, whereas the recommended timepoints for evaluation of haematology and serum chemistry are within approximately 1–3 days following the first and last dose administration, at the end of the recovery period and pre-dosing. This issue also applies for the platform-based toxicity studies. In the Days 120 responses, the applicant justified the lack of interim analysis of haematology and serum due to their little value to the overall risk assessment. Further, the applicant stated that clinical pathology evaluation one day after the last dose was considered as a worst-case scenario and enabled a direct correlation to histopathological findings. The applicant’s justification was considered adequate by the CHMP.

mRNA-1345-related macroscopic findings were observed at the injection site consisted of swollen muscle occasional together with firm material to muscle and/or subcutaneous tissues. Sporadically, animals dosed with mRNA-1345 had enlarged or abnormal consistency of the regional draining iliac and popliteal lymph nodes and sciatic nerves. Furthermore, mRNA-1345-related organ weight increases were observed in the spleen of both sexes. mRNA-1345-related microscopic findings were observed at the injection site, which were characterised by mild to moderate acute inflammation with mixed cell, subcutaneous oedema, and/or increased incidence of minimal myofiber necrosis with minimal to mild inflammatory infiltrates. Minimal to mild mixed cell inflammation was also observed in the right gastrocnemius muscle of animals. This finding was considered to be an extension of the inflammation observed in the right quadriceps muscle as the right gastrocnemius muscle was not injected during the course of this study. In addition, the draining lymph nodes had minimal to moderate neutrophilic to mixed cell inflammatory infiltrates in the perinodal adipose tissues with increased macrophages in the lymphoid sinuses. Moreover, a decrease in lymphoid cellularity was observed in the white pulp of spleen and fascial and epineural tissues of the right sciatic nerves were infiltrated predominantly with neutrophils. These findings were considered likely a local extension of the inflammatory changes at the injection site.

In general, a comprehensive list of organs/tissues was microscopically evaluated. Nevertheless, an assessment of the bronchi (main stem), larynx, oviducts and Peyer's patches was not conducted, which are not in line with the WHO guideline on the nonclinical evaluation of vaccines (WHO 2005). However, lack of larynx assessment is considered acceptable since it was evaluated in the platform-based studies. In the Day 120 responses, the applicant explained that the selected organs/tissues were based on previous non-clinical and clinical experience with the vaccine components. The response given by the applicant is considered acceptable by the Committee.

Moreover, specific antibody titres were detected in all vaccinated animals. However, antibody response was evidently higher in females for all RD-toxicity studies. In the Day 120 responses, the applicant explained that the animals were dosed on a µg per dose basis, rather than a µg per kg basis. The markedly higher antibody response in females was explained by the fact that females had less body weight, therefore on a mg/kg basis received higher doses than males. The justification provided by the applicant is considered acceptable.

In addition, a non-GLP-compliant pilot toxicity study was conducted in male and female rats to evaluate mRNA-1345 at dose levels of 15, 50, or 100 µg via two intramuscular injections within 3 weeks and additional 2-week recovery period. No mRNA-1345-related mortalities were observed in the animals. A transient decrease in mean body weight gain was observed in rats at ≥50 µg/dose, which resolved within one week after the first dose. mRNA-1345-related findings included clinical observations consisting of transient local effects of oedema and impaired limb function at the injection site, and changes in clinical pathology parameters that were consistent with an inflammatory response and mild effects in the liver. A post-mortem analysis of the study animals was not conducted. Overall, this study has several major limitations (e.g. animal number/group, only in-life endpoints). Thus, this study is considered only as supportive by the CHMP.

The observed findings in the mRNA-1345 toxicity studies were comparable to those in the other platform toxicity studies. These platform repeat-dose toxicity reports were already submitted for the initial marketing authorisation of Spikevax. All doses administered were clinically tolerated across the mRNA vaccine platform studies. Test article-related, generally dose-dependent, clinical pathology and cytokine changes were observed at ≥8.9 µg/dose and were consistent with a transient local and/or systemic inflammatory or immune response. Reversible or reversing erythema and oedema at the injection site and transient increases in body temperature at 6 hours after dosing, returning to baseline 24 hours after dosing, were observed. Occasionally, hindlimb impairment and/or vocalisation attributed to injection site effects were observed. Haematology changes included increases in white blood cells, neutrophils, and eosinophils and decrease in lymphocytes; coagulation changes included increases in fibrinogen and activated partial thromboplastin time; and clinical chemistry changes included decreases in albumin, increases in globulin, and a corresponding decrease in the albumin/globulin ratio. Clinical pathology changes generally reversed or were reversing by the end of the 2-week recovery period. Test article-related transient cytokine increases were observed at ≥8.9 µg/dose at 6 hours after dosing, including interferon γ-induced protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 alpha. Cytokine changes were generally reversing by the end of the 2-week recovery period.

In necropsy and pathology analysis, test article-related and dose-dependent changes in organ weights, macroscopic and microscopic findings were observed at ≥8.9 µg/dose. Organ weight increases were observed in the spleen, liver, and adrenal gland. Organ weight changes were generally reversing by the end of the 2-week recovery period. Macroscopic changes included skin thickening at the injection site and enlarged lymph nodes. Injection site changes completely recovered, and lymph node changes were recovering by the end of the 2-week recovery period. Microscopic changes included mixed-cell inflammation at the injection site; increased cellularity and mixed-cell inflammation in the inguinal, iliac, and popliteal lymph nodes; decreased cellularity in the splenic periarteriolar lymphoid sheath;

increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy in the liver. Microscopic changes were generally reversing by the end of the 2-week recovery period.

Of importance, several other concerns were identified and properly addressed by the applicant during the assessment of Spikevax for marketing authorisation, e.g. increases in eosinophil counts (up to 6.5-fold compared to the control groups) were consistently observed in the haematology samples taken after the last booster administrations. Increased eosinophil/eosinophilia counts can be correlated with diseases such as IgE-mediated type-1 allergy, in which peripheral eosinophils are increased as a consequence of the late-phase allergic reaction, and asthma. The observed eosinophil increase in rat LNP-mRNA studies could therefore be potentially clinically relevant. Furthermore, increases in activated partial thromboplastin time (APTT, up to ~30%) and fibrinogen (up to ~2.5-fold) were consistently observed in rat repeat-dose toxicity studies. These haemostatic alterations could potentially be clinically relevant. However, the toxicological potential of these rat findings is low for humans. Considering these aspects, these findings are included in the SmPC for Spikevax. Taken into account that the same platform-studies were submitted for the MAA of mRNA-1345 and similar findings were seen in repeat-dose toxicity studies with mRNA-1345 (study number 1021-9921 and 2308-121), same wordings in section 5.3 in SmPC for the mRNA-1345 has been included.

Overall, the toxicological results with mRNA-1345 were consistent with the platform toxicity data, and mRNA-1345 was well tolerated in rats. The repeat-dose toxicity study programme is considered adequate by the CHMP.

2.5.3.3. Genotoxicity

Table 1: Overview of genotoxicity studies:

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Ames test, GLP Study 9601567 and 9601035	S. typhimurium E. coli	+/- S9 1.58 – 5,000 µg/plate	SM-102: negative PEG2000-DMG: negative
In vitro Mammalian Cell Micronucleus Test, GLP Study 9601568 and 9601036	human peripheral blood lymphocytes	+/- S9 3.25 - 500 µg/mL	SM-102: negative PEG2000-DMG: negative
Mammalian Erythrocyte Micronucleus Test, *in vivo*, GLP Study 9800399	Rat, bone marrow	Single IV dose mRNA-1706/LNP vaccine: 0.6, 1.3, or 2.6 mg/kg RNA (females); 1.3, 2.6, or 5.2 mg/kg RNA mg/kg (males)	mRNA-1706: positive
Mammalian Erythrocyte	Rat, bone marrow	Single IV dose NPI luciferase mRNA/LNP: 0.32/6, 1.07/20, or	NPI luciferase mRNA: negative

Micronucleus Test, *in vivo*, non-GLP Study af87fu-125012nglpich-btl		3.21/60 mg/kg RNA	

The conducted genotoxicity studies were already submitted for the initial marketing authorisation of Spikevax Covid-19 mRNA vaccine formulated with the same LNPs as in mRNA-1345, except of the *in vitro* genotoxicity studies with PEG2000-DMG (GLP-compliant Ames test and micronucleus tests in human peripheral blood lymphocytes). The GLP-compliant Ames tests in Salmonella typhimurium and Escherichia coli and *in vitro* micronucleus tests in human peripheral blood lymphocytes for the LNP components SM-102 and PEG2000-DMG were negative for mutagenicity. To support the use of SM-102 lipid and PEG2000-DMG in LNP-formulated mRNA-based drug products, one GLP-compliant study and another non-GLP-compliant *in vivo* erythrocyte micronucleus study were completed in bone marrow from rats applying an IV route of administration, using representative mRNA drug products formulated in the same LNPs then mRNA-1345. Results from non-GLP-compliant micronucleus studies were negative for clastogenicity, while results from the GLP-compliant *in vivo* study were weakly positive for clastogenicity. Significant increases in micronucleated immature erythrocytes were observed in male rats at both 24 and 48 hours and in females at 48 hours only, but there was no clear dose response after IV administration. Thus, the applicant considers the *in vivo* erythrocyte micronucleus test data as equivocal. The company assumes that the totality of toxicological and genotoxicity data with mRNA-1345 and other mRNA vaccines in an SM-102-containing LNP matrix indicate that these equivocal results are likely driven by micronuclei formation secondary to elevated body temperature induced by LNP-induced systemic inflammation and cytokines at high systemic (IV) doses. Overall, the company considers the genotoxic risk to humans to be low for SM-102-containing mRNA vaccines due to minimal systemic exposure following intramuscular administration, limited duration of exposure, negative *in vitro* results, and equivocal *in vivo* results.

The applicant's position is supported that an intramuscular administration of a vaccine from the company's mRNA platform, such as mRNA-1345, has a very low genotoxic risk to human.

The applicant summarised the genotoxicity study results in the SmPC section 5.3 in alignment with the Spikevax vaccine, as agreed with the Committee.

2.5.3.4. Carcinogenicity

Consistent with the WHO regulatory guidelines on the nonclinical evaluation of vaccines (WHO 2005), no carcinogenicity studies were conducted with mRNA-1345. This is accepted by the CHMP.

2.5.3.5. Reproductive and developmental toxicity

In respect to the planned indication of mRNA-1345 to active immunise adults 60 years of age or older, a DART study is normally not requested. Nevertheless, a GLP-compliant combined developmental and perinatal/postnatal developmental and reproductive toxicity study was conducted to assess the potential effects of mRNA-1345 on fertility and pre- and postnatal development in pregnant and lactating female Sprague Dawley rats. Dams were administered via IM injection 4 doses of 96 µg/dose mRNA-1345 prior to mating and during gestation period. F0 female rats were divided into either caesarean-sectioning phase cohort (Cohort 1, euthanised on GD 21) or natural delivery phase cohort

(Cohort 2, euthanised LD 21). All F1 pups assigned to Cohort 2 were euthanised on Day 13 or 21 postpartum.

There were no mRNA-1345-related differences in mean body weight or gravid uterine weight, no vaccine-related effects on the number and length of oestrous cycles, mating, fertility, or pregnancy indices. No macroscopic findings or effects on any ovarian and uterine parameters, or foetal litter observations or incidence of foetal external, visceral, or skeletal malformations, including skeletal ossification site averages, were observed. In addition, administration of mRNA-1345 did not affect any natural delivery, litter observations, or any F1 generation preweaning parameter (e.g., clinical observations, body weights, and pup gross necropsy examination), including reflex and development.

Clinical signs in mRNA-1345-dosed F0 dams were transient and considered a result of the intramuscular injection, including limited use of and swollen hindlimbs, which resolved within 1 week after dosing. Furthermore, mean body weight gain was reduced in the week after mRNA-1345 administration, which rebounded following resolution of the hindlimb discomfort. Within the lactation period, mean maternal body weight gain was generally reduced, which correlated with decreased mean maternal food consumption. Scabbed skin and thin cover fur on the hindlimbs were present in both control and mRNA-1345-dosed animals and were considered secondary to injection. The clinical signs persisted into the gestation period, and there was a low incidence of lack of pinch reflex, which correlated with the limited usage of the hindlimb, and skin abrasion along the hindlimb in females during this period. None of these findings were considered adverse, which is agreed.

Anti-RSV antibodies were detected in the maternal F0 generation serum samples after the first vaccination and remained detectable through end of study (Lactation Day 21). Anti-RSV antibodies were also detected in foetal F1 serum samples (at Gestation Day 21 and Lactation Day 21) and maternal F0 generation milk samples, demonstrating effective placental and lactation transfer of anti-RSV antibodies to offspring when females are immunised prior to and after mating.

In total, administration of mRNA-1345 at 96 µg/dose during the premating period (28 and 14 days prior to mating) and on Gestation Days 1 and 13 was clinically tolerated and did not result in any adverse observations in F0 or F1 generation rats.

The applicant summarised the DART study results in the SmPC section 5.3 in alignment with the Spikevax vaccine, as agreed with the Committee.

2.5.3.6. Toxicokinetic data

No toxicokinetic data have been recorded with mRNA-1345 during the toxicity studies. This is accepted by the CHMP.

2.5.3.7. Local Tolerance

No dedicated local tolerance studies have been performed with mRNA-1345. Local tolerance was analysed within repeat-dose toxicity studies. Transient oedema and erythema were observed after vaccine administration, which were in general resolved within one week. These findings together with the macroscopic and microscopic pathology findings indicates transient local inflammation. The provided analysis on local tolerance is considered adequate by the CHMP.

2.5.3.8. Other toxicity studies

No other toxicity studies have been conducted with mRNA-1345. This is accepted by the CHMP.

2.5.4. Ecotoxicity/environmental risk assessment

The applicant did not conduct environmental risk assessment (ERA) studies on mRNA-1345. The mRNA drug substance in mRNA-1345 vaccine is composed of naturally occurring nucleosides and sugars and is degraded to natural metabolic products before excretion and to natural transformation products in the environment. Therefore, the prescribed use of mRNA-1345 vaccine does not significantly alter the concentration or distribution of mRNA building blocks and their degradants in the environment. Furthermore, toxicological data in mammalian species show no population relevant alerts. Therefore, it is concluded that due to its nature mRNA-1345 is unlikely to result in a significant risk to the environment and ERA studies are not required. This justification is sufficient and in compliance with EMA guideline EMEA/CHMP/SWP/4447/00 Corr 2.

The LNP matrix used to formulate mRNA-1345, which is comprised of two synthetically derived lipid excipients (SM-102 and PEG2000-DMG) as well as cholesterol and DSPC, has also been used in other respiratory mRNA vaccines manufactured by the applicant, including the authorised Spikevax vaccine for the prevention of Covid-19. Due to the nature and toxicological properties of the lipid excipients in this LNP matrix, it is concluded that they are unlikely to result in a significant risk to the environment following the prescribed use of mRNA-1345 vaccine.

In conclusion, the CHMP is of the view that the prescribed use of mRNA-1345 is of no immediate concern for the environment.

2.5.5. Discussion on non-clinical aspects

Pharmacology

The applicant conducted nonclinical primary pharmacology studies in Balb/c mice and cotton rats where the immunogenicity (mice, cotton rats) and efficacy (cotton rats) of mRNA-1345 were evaluated. Data from these studies indicate the ability of this vaccine to induce neutralising, PreF-biased antibodies, and Th1-secreting CD4+ and CD8+ T-cells, and to prevent the vaccinated cotton rats from RSV challenge. The immunological profile induced by mRNA-1345 is characteristic of protection without enhanced lung inflammation and Th2 cytokines after RSV challenge. Overall, the nonclinical primary pharmacology evaluation is adequate. A few issues of other concerns have been clarified in the applicant's responses at Day 120.

The absence of the secondary pharmacodynamics studies, stand-alone safety pharmacology studies, and pharmacodynamics drug interaction studies is in line with the regulatory guidelines and thus acceptable to the Committee.

Pharmacokinetics

The applicant submitted a non-GLP-compliant biodistribution study conducted with a similar product (mRNA-1647) to help understand the kinetic and tissue distribution of mRNA-1345. It is noted that PEG2000 is increased 2-fold in the LNP matrix formulation included in mRNA-1345 compared to LNPs matrix included in mRNA-1647. It is not expected to result in different cleavage rate *in vivo* or different kinetics and distribution in systemic circulation and tissues, as adequately discussed in the applicant's Day 120 response. The proposed use of a platform approach is acceptable.

In addition, the applicant evaluated the metabolism of SM-102-containing LNP matrix *in vivo* and *in vitro*, while the excretion characteristics were characterised *in vivo*. These data indicate the extensive metabolisation of SM-102 through ester hydrolysis and β-oxidation, leading to rapid *in vivo* clearance of SM-102 and its metabolites. Data from these studies provide initial insight into the metabolism and excretion characteristics of SM-102 *in vivo*, supporting the assumption that SM-102 is unlikely to

accumulate on repeat IM dosing or be a risk for elimination in patients with hepatic or renal insufficiency. A few issues of other concerns have been clarified in the applicant's responses at Day 120.

The absence of PK drug interaction studies and other PK studies conducted with mRNA-1345 is in line with regulatory guidelines and thus acceptable by the CHMP.

Toxicology

The company conducted a complete toxicity study programme with mRNA-1345 including GLP-compliant repeat-dose toxicity study, a non-GLP-compliant pilot toxicity study and a GLP-compliant DART study in Sprague Dawley rats. In addition, GLP-compliant repeat-dose toxicity and genotoxicity data from the company's mRNA vaccine platform was submitted, using similar mRNA-based vaccines formulated in same LNPs encoding for different antigens (ZIKV vaccines: mRNA-1706 and mRNA-1893, hMPV and PIV3 vaccine: mRNA-1653, and CMV vaccines: mRNA-1647 and mRNA-1443). Given the consistency of observed findings across the toxicity studies using different mRNA vaccines, it is concluded that the toxicities associated with mRNA vaccines formulated in LNPs are driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine.

In the repeat-dose toxicity studies, all doses and dose levels of analysed mRNA vaccines were clinically tolerated across the mRNA vaccine platform studies. Test article-related, dose-dependent clinical pathology and cytokine changes were observed and were consistent with a transient local and/or systemic inflammatory or immune response. In post-mortem analysis, transient increased spleen, liver, and adrenal gland, mixed-cell inflammation at the injection site and draining lymph nodes, decreased cellularity in the lymphoid sheath, increased myeloid cellularity in the bone marrow, and hepatocyte vacuolation and Kupffer cell hypertrophy in the liver. All findings were generally fully recovered or showed signs of recovery by the end of the 2-week recovery period.

The applicant conducted a standard battery of genotoxicity studies. In the *in vitro* bacterial and mammalian test, SM-102 and PEG2000-DMG were negative for mutagenicity. The *in vivo* erythrocyte micronucleus tests in rat bone marrow were equivocal. Thus, the genotoxic risk to humans is low for SM-102-containing LNP-matrix mRNA vaccines due to minimal systemic exposure following intramuscular administration.

In a GLP-compliant combined DART study with mRNA-1345 in SD rats, no adverse toxicity was observed for fertility, mating, perinatal and postnatal developmental. Furthermore, anti-RSV antibodies were detected in foetal F1 serum samples and maternal F0 generation milk samples, demonstrating effective placental and lactation transfer of anti-RSV antibodies to offspring when females are immunised prior to mating and during gestation.

In conclusion, the conducted toxicity studies are considered adequate by the CHMP.

2.5.6. Conclusion on the non-clinical aspects

The pharmacology and toxicology studies performed are in line with the WHO Guidelines. The absence of single-dose toxicity studies, carcinogenicity studies and an environmental risk assessment is acceptable to the CHMP. The applicant has provided acceptable responses to the concerns raised by the Committee; therefore, the non-clinical package can now be considered acceptable in support of the MAA.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Study Number (Country)	**Study Design**	**Study Population(s)**	**Regimen**	**Number of Participants Exposed**	**Efficacy and Immunogenicity Objective(s)**	**Safety Objective(s)**
mRNA-1345-P301 (Global)[a]	Phase 2/3, randomised, observer-blind, placebo-controlled, case-driven pivotal safety and efficacy study	Adults ≥60 years of age with or without underlying medical conditions	Single IM injection: mRNA-1345 50 µg Placebo (0.9% normal saline) 1:1 randomisation, stratified by age (60 to 74 years or ⩾75 years) and presence or absence of CHF and/or COPD as prespecified risk factors for LRTD	mRNA-1345=18,245 Placebo=18,184	Primary Efficacy: • To evaluate the efficacy of a single injection of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 12 months postinjection. Key Secondary Efficacy: • To evaluate the efficacy of a single injection of mRNA-1345 vaccine in the prevention of the first episode of RSV-ARD as compared with placebo within the period of 14 days postinjection up to 12 months postinjection. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalisation associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 12 months postinjection. Other Secondary Efficacy:	• To evaluate the safety and tolerability of the mRNA-1345 vaccine

Study Number (Country)	Study Design	Study Population(s)	Regimen	Number of Participants Exposed	Efficacy and Immunogenicity Objective(s)	Safety Objective(s)
					• To evaluate the efficacy of a single injection of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo by RSV subtype. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 24 months postinjection.	
mRNA-1345-P101 (US)[b]	Phase 1, randomised, 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	Single IM injection: mRNA-1345 50 µg mRNA-1345 100 µg mRNA-1345 200 µg Placebo (0.9% normal saline) 3 IM injections (Day 1, 57, 113): mRNA-1345 100 µg Placebo (0.9% normal saline)	Single injection: 50 µg=19 100 µg=20 200 µg=20 Placebo=15 3 injections: 100 µg=20 Placebo=5	Immunogenicity: • To evaluate the Ab response to each vaccine dose level in adults 18 to 49 years of age, adults 65 to 79 years of age, and adults of Japanese descent ⩾60 years of age. • To evaluate the Ab response to both 1 and 3 vaccine injections in adults 18 to 49 years of age at the middle dose level of mRNA-1345. • To evaluate the Ab response to a vaccine booster injection given approximately 12 months after the primary injection in adults 65 to 79 years of age.	• To evaluate the tolerability and reactogenicity of up to 5 dose levels of mRNA-1345 in adults 18 to 49 years of age, adults 65 to 79 years of age, and adults of Japanese descent ⩾60 years of age. • To evaluate the tolerability and reactogenicity of 3 injections of the middle dose level of mRNA-1345 given 56 days apart in adults 18 to 49 years of age. • To evaluate the tolerability and reactogenicity of a booster injection of mRNA-1345 given approximately 12 months after
		Healthy adults 65 to 79 years of age	First IM injection + booster (~12 months later): mRNA-1345 12.5 µg mRNA-1345 25 µg mRNA-1345 50 µg mRNA-1345 100 µg mRNA-1345 200 µg	Single injection: 12.5 µg=48 25 µg=48 50 µg=47 100 µg=48 200 µg=48 Placebo=59 Booster injection: Subset of single injection groups received identical booster injection		

			Placebo (0.9% normal saline)			the primary injection in adults 65 to 79 years of age.
		Healthy adults of Japanese descent >60 years of age	Single IM injection: mRNA-1345 (100 µg) Placebo (0.9% normal saline)	100 µg=21 Placebo=4		
mRNA-CRID-001 (US)	Phase 1b randomised, open-label, multicentre study to evaluate the safety, reactogenicity and immunogenicity of modified mRNA vaccines using a systems biology approach	Adults 18 to 75 years of age	Single IM injection: mRNA-1345 (50 µg)	50 µg=61 Cellular immunogenicity subset=30 (15 between 50 to 75 years of age; 15 between 18 to 49 years of age)	Exploratory Immunogenicity: To assess and characterise cellular, humoral, and mucosal immune responses, and peripheral blood cellular and plasma biomarkers to identify molecular mechanisms of mRNA vaccines.	Not included in this application

Abbreviations: Ab = antibody(ies); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRID = clinical research for infectious diseases; CRO = contract research organisation; DBL = database lock; IM = intramuscular(ly); LRTD = lower respiratory tract disease; mRNA = messenger ribonucleic acid; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; US = United States.

Participants remain in all studies to all protocol-specified assessments of efficacy, immunogenicity, and safety through the scheduled end of study.

a. Only select Moderna and CRO personnel were unblinded to support this application. Study P301 Primary Analysis data cutoff date was 30 Nov 2022 (DBL date: 25 Jan 2023) and the Additional Analysis data cutoff date was 30 Apr 2023 (DBL 02 Jun 2023).

b. Only select Moderna and CRO personnel were unblinded to support this application. Study P101 data cutoff dates were 27 Sep 2021 (adults 18 to 49 years of age); 03 Oct 2022 (adults 65 to 79 years of age); 13 Sep 2022 (Japanese adults ≥60 years); DBL date: 06 Feb 2023.

A number of clinical trials sites have undergone GCP inspection, however, not all the reports are currently available, cf. section 2.6.7 (cf letter of undertaking).

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2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for RSV mRNA-1345 candidate vaccine. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current the Guidelines on clinical evaluation of vaccines.

2.6.2.2. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

Mechanism of action

mRNA-1345 is an LNP-encapsulated mRNA-based vaccine encoding the membrane-anchored RSV F-glycoprotein, derived from an RSV-A strain (RSV-A A2 strain), and stabilised in the prefusion conformation through structural engineering. The F protein exists in 2 primary conformational states, the prefusion state facilitates entry into the host cell through a conformational change to the postfusion state. The F protein was selected as the vaccine antigen due to its role in host cell entry and because it is highly conserved across RSV-A and RSV-B subtypes. The prefusion conformation was selected because it displays all the epitopes known to elicit nAbs and is the primary target of the nAb response following RSV exposure.

Vaccine efficacy results against RSV-LRTD and RSV-ARD are presented in the interim analysis CSR from Study P301. Clinical development of mRNA-1345 includes the assessment of immune responses induced by mRNA-1345 as presented in Study P101 and Study CRID-001.

Primary and Secondary pharmacology

The bioanalytical methods used to support the clinical development of RSV mRNA-1345 vaccine are depicted in the below table.

Detection of infection with RSV and/or other respiratory pathogens using GenMark Diagnostics' FDA cleared and CE marked ePlex® Respiratory RP panel. The GenMark ePlex RP panel is a multiplexed nucleic acid test intended for the simultaneous qualitative detection and differentiation of nucleic acids from 17 viral and bacterial respiratory organisms in nasopharyngeal swabs. The assay is commercially available and was verified in two selected laboratories for the use in Study P301:

- Additional RT-PCR assay for SARS-CoV-2 infection evaluation. The SARS-CoV-2 nucleic acid amplification assay is a real-time (TaqPathTM) RT-PCR assay for detection and quantification of SARS-CoV-2 genomic RNA in nasopharyngeal swabs.

- RSV antibody quantification using assays developed and qualified for this programme:
    - Quantification of binding antibodies to RSV PreF and PostF proteins. This Luminex® based quantitative multiplexed assay was used for the detection of IgG antibodies to RSV PreF and PostF antigens in human serum.
    - Quantification of RSV-A and RSV-B nAbs. This microneutralisation quantitative assay was used to measure the nAbs against RSV subtypes: A (Virus strain A2) and B (Virus strain 18537) in human serum.
- RSV T-cell quantification using assays developed for this programme:
    - RSV PreF-specific CD8+ and CD4+ T cells producing type 1 and/or type 2 cytokines were measured in a fit-for-purpose ICS assay developed by Moderna.

- **Overview of bioassays for the assessment of clinical endpoints**

Assay Name	Methodology	Study Number	Context of Use	Assay Status (Vendor)
ePlex Respiratory Pathogen Panel	RT-PCR	P301	RSV-A or RSV-B (or other respiratory pathogens) infection	Verified (Eurofin-Viracor)
SARS-CoV-2 infection evaluation	RT-PCR	P301	SARS-CoV-2 infection	Validated (Eurofin-Viracor)
Quantification of anti-RSV-A and -B neutralizing antibody	Microneutralization (VAL117)	P101 P301	Humoral immunogenicity assessment	Qualified (P101) Validated (P301) (Viroclinics DDL)
Quantification of anti-RSV PreF and PostF binding antibody	Multiplex Luminex (VSDVAC69)	P101 P301	Humoral immunogenicity assessment	Qualified (P101) Validated (P301) (PPD Laboratories)
RSV CD4+ and CD8+ T cell response	Flow-cytometry and ICS	CRID-001	Cellular immunogenicity assessment	Developed (Moderna Research)

Abbreviations: ICS=intracellular cytokine staining; PreF=prefusion; PostF=postfusion; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase polymerase-chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Note: Assay status is defined as follows: "developed" defines the design, operating conditions, limitations, and suitability of the assay to ensure that the assay is optimised for validation; "qualified" qualifies the assay's performance for the analysis of study samples to support early drug development; "validated" proves that the optimised assay is suited for the analysis of the study samples to support regulatory decision making such as effectiveness of the product; and "verified" is when a laboratory demonstrates that it can satisfactorily perform the assay within the assay's defined/validated parameters.

2.6.3. Discussion on clinical pharmacology

No human pharmacokinetic studies have been performed. This can be agreed upon as pharmacokinetic studies are not usually required for vaccines.

The applicant utilised RT-PCR assays for the pivotal Study P301 and other assays to evaluate humoral and cellular immunogenicity. The GenMark ePlex RP panel is a commercially available RT-PCR assay that was verified in the two laboratories used for confirmation of RSV-infection which is acceptable.

Assays have been developed for the detection of infection with RSV and other respiratory pathogens using an FDA cleared and CE marked test (GenMark Diagnostics' ePlex® Respiratory Pathogen Panel). In addition, assays to quantify RSV antibodies binding to RSV PreF and PostF proteins, RSV-A and RSV-B neutralising antibodies as well as and assay to determine RSV PreF specific CD8+ and CD4+ T cell responses have been developed.

The ePlex® Respiratory Pathogen Panel (RP1) is a qualitative, automated, *in vitro* diagnostic test to be used for the qualitative detection and identification of nucleic acids from 17 respiratory pathogens in nasal and nasopharyngeal swabs obtained from individuals suspected of respiratory tract infections. The test system is based on multiplex PCR amplification of extracted nucleic acids followed by detection of amplified products on The True Sample-to-Answer Solution® ePlex instrument. Pathogens detected by the test are listed. A correlation and method comparison (inter-laboratory comparison) for GenMark Dx ePlex® RP1 assay in nasopharyngeal swabs was performed by Eurofins Viracor Laboratories for samples assessed in the USA site and for samples assessed in the Eurofins-ECL

located in the Netherlands or Singapore. Performance of the GenMark ePlex® Respiratory Pathogen Panel has been verified at the Netherlands and the Singapore sites. The Inter-laboratory comparison was performed to demonstrate concordance between laboratory test results. Clinical samples provided by Eurofins Viracor USA were analysed by ECL Breda and ECL Singapore and compared against the Eurofins Viracor assigned value. Some contradictory results are described in the analysis of clinical samples in the inter-laboratory comparison evaluations. The applicant has discussed the contradictory results and in this regard comment on handling and storage of samples at the different sites. Contradictory results are in several cases explained by signal likely being near the LOD. A quantitative multiplexed Luminex technology assay was used for the detection of IgG antibodies to RSV PreF and PostF antigens in human serum. The assay has been qualified to establish the assay operating characteristics, to evaluate the precision and ruggedness, and to assess the dilutional linearity, specificity, selectivity, and relative accuracy of the RSV2-plex assay.

A quantitative neutralisation assay was used to measure the neutralising antibodies against RSV subtypes: A (Virus strain A2) and B (Virus strain 18537). The RSV A and B Neutralisation Assay was validated for specificity, accuracy, precision, linearity dilutional linearity, stability, robustness, end-of-run-analysis and stability of serum samples stored at 18-22°C or 2-8°C. However, according to the applicant, the anti-RSV-A and B assays used for the phase 1 mRNA-1345 P101 study were qualified. This is acceptable for the phase I study which is early in clinical development. However, it is unclear if the validation report provided for this neutralisation assay relates to the phase 3 study mRNA-1345-P301, for which no immunogenicity data have been submitted in the initial submission. The immunogenicity data from Study P301 have been provided in the applicant's D120 responses, including information on the immunogenicity assays.

The applicant has clarified that for the Phase 1 clinical trial (P101 study), a "fit for purpose" assay validation for RSV A and B neutralisation assays was performed using commercially available samples. Also, CMI data was not collected or analysed in the P301 pivotal efficacy trial, and available data for CMI pertains to study CRID-001 only.

An ICS assay was used to measure RSV PreF-specific CD8+ and CD4+ (Th1 and Th2) T cell responses induced by mRNA-1345 vaccine in clinical samples collected in Study CRID-001. The assay has not been qualified or validated. In the applicant's Day 120 responses, was provided a description on the development pathway of the intercellular cytokine stain flow cytometry assay used for CMI analysis. The assay was conducted on PBMC samples collected at baseline and additional 4 times in a network of applicant's approved PBMC collection sites utilising applicant approved PBMC isolation SOP. All CMI samples (timepoints) from every participant were tested in one flow cytometry assay run and testing completed by one analyst, hence eliminating any differences that may arise due to assay variation. During testing, each sample was stimulated with PMA/Ionomycin (positive stimulation) as well as with DMSO (negative stimulation/background). Data was reported after subtracting the background, thus confirming that the reported T cell responses were specific to RSV Pre-F antigen (mRNA-1345). However, caution may need to be exercised when interpreting these data, because the assay used in this study was not validated.

2.6.4. Conclusions on clinical pharmacology

The immunogenicity results are supportive for the current application, however in the initial submission only information regarding immunogenicity assays used in the phase I clinical study have been provided (mRNA-1345-P101).

In the D120 responses, the applicant provided further information on the immunogenicity assays used in the pivotal phase 3 clinical study (mRNA-1345-P301) and the corresponding validation reports.

The immunogenicity data from Study P301 have been also provided in the applicant's D120 responses, which is acceptable to the CHMP.

2.6.5. Clinical efficacy

The report summarises results of a Phase 2/3, randomised, observer-blind, placebo-controlled, case driven, multi-centre, multi-country study (Study P301) in adults ≥60 years. The study started on 17 Nov 2021 with the Phase 2 segment, which assessed the tolerability and safety of the 50 µg mRNA-1345 dose that had been selected based on safety and immunogenicity data from the Phase 1 study (P101). An unblinded DSMB review of the Day 29 safety data (planned for the first 400 Phase 2 participants) included 1115 participants, of whom 490 had ≥28 days of safety follow-up (data cut-off date of 24 Jan 2022). The DSMB issued a positive recommendation on 21 Feb 2022 and the study was cleared to proceed to the Phase 3 segment. In total, 35,541 participants were randomised in the Phase 2 and 3 segments of Study P301 as of 31 Oct 2022 (enrolment cut-off date for this analysis). Participants in both the Phase 2 and Phase 3 segments are presented as one dataset since participants were randomised, injected, and followed in the same manner (apart from a Day 15 blood draw in the Phase 2 segment) as part of the seamless Phase 2/3 study design.

2.6.5.1. Dose response study(ies)

Study mRNA-1345-P101 (referred to as Study P101) is a phase 1, randomised, observer-blind, placebo-controlled, dose escalation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus (RSV), in healthy younger adults aged 18 to 49 years, women of child-bearing potential aged 18 to 40 years, healthy older adults aged 65 to 79 years, Japanese older adults aged ≥60 years, and RSV-seropositive children aged 12 to 59 months.

Study P101 data permitted selection of an mRNA-1345 dose level and vaccination schedule for subsequent clinical development in adults.

2.6.5.2. Main study(ies)

A Phase 2/3, Randomised, 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, referred to as Study P301.

Methods

Study Participants

Inclusion criteria for the study population included adults ≥60 years of age, an age group known to be at risk for RSV-LRTD. Participants were permitted to have one or more chronic medical diagnoses (including CHF [including heart failure with preserved ejection fraction] and COPD), if considered stable. This was intended to assess the activity of mRNA-1345 in populations known to be at higher risk of RSV-LRTD than adults without such chronic cardiopulmonary conditions.

Exclusion criteria were applied to protect participant safety and to ensure that efficacy, safety, and immunogenicity endpoints could be assessed. Exclusion criteria included history of myocarditis, pericarditis, or myopericarditis within 2 months prior to screening; autoimmune condition requiring systemic immunosuppressants (stable HIV-positive participants were permitted); history of serious reaction to any prior vaccination; and receipt or planned receipt of non-study vaccination within 28 days before or after Day 1 injection.

Treatments

Participants in the Phase 2 and in the Phase 3 segments were randomised to receive either 50 µg mRNA-1345 vaccine or placebo in a 1:1 ratio. Efficacy over a period of up to 24 months shall be demonstrated.

Objectives

The interim analysis CSR summarises data regarding the primary safety and efficacy objectives detailed in the Table 2 (below) from the first planned IA. Data regarding the key secondary objective related to VE against RSV ARD and the secondary objective related to VE against RSV by subtype are also summarised.

The CHMP noted that data regarding the other secondary, additional exploratory, and immunogenicity objectives will be followed as RECs.

Table 2: Primary and secondary objectives and endpoints

Objectives	Endpoints
Primary Safety and Efficacy Objectives	
Safety: To evaluate the safety and tolerability of the mRNA-1345 vaccine.	Numbers and percentages of participants with solicited local and systemic ARs up to 7 days postinjection. Unsolicited AEs up to 28 days postinjection. MAAEs, AESIs, SAEs, and AEs leading to withdrawal up to 24 months postinjection.
Efficacy: To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD[a] as compared with placebo within the period of 14 days postinjection up to 12 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days postinjection up to 12 months postinjection. Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days postinjection up to 12 months postinjection.
Key Secondary Efficacy Objectives	
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-ARD[a] as compared with placebo within the period of 14 days postinjection up to 12 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days postinjection up to 12 months postinjection.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 12 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days postinjection up to 12 months postinjection.

Other Secondary Efficacy Objectives	
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause hospitalizations as compared with placebo within the period of 14 days postinjection up to 12 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days postinjection up to 12 months postinjection.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of all-cause LRTD as compared with placebo within the period of 14 days postinjection up to 12 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent all-cause LRTD within the period of 14 days postinjection up to 12 months postinjection.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 24 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days postinjection up to 24 months postinjection. Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days postinjection up to 24 months postinjection.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo by RSV subtype.	Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD by RSV subtype A and RSV subtype B.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 24 months postinjection.	Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days postinjection up to 24 months postinjection.
To evaluate the efficacy of a single dose of mRNA-1345 vaccine on the change from baseline in frailty status at 12 months and 24 months.	Change in total frailty score from baseline to 12 months and 24 months postinjection, using the EFS.

Objectives	Endpoints
Immunogenicity Objective	
To evaluate the Ab response to a single dose of mRNA-1345 vaccine from baseline up to 24 months postinjection.	GMT of serum RSV-neutralizing Abs and GMC of serum RSV-binding Abs at prespecified study timepoints from baseline up to 24 months postinjection. SRR in RSV-neutralizing Abs up to 24 months postinjection. GMFR from baseline at prespecified study timepoints up to 24 months postinjection. Proportion of participants with ≥2-fold increase in Ab titer from baseline at prespecified study timepoints up to 24 months postinjection.

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EFS = Edmonton Frail Scale; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; LRTD = lower respiratory tract disease; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; SAE = serious adverse event; SRR = seroresponse rate.

[a] Case definitions for efficacy endpoints are provided in Section 3.4.2.1.

Participants in both the Phase 2 and Phase 3 segments contributed to the planned safety and efficacy analyses. Two primary efficacy endpoints were assessed starting 14 days postinjection, and for the period up to 12 months postinjection:

- VE measured against the first occurrence of RSV-LRTD with 2 or more symptoms
- VE measured against the first occurrence of RSV-LRTD with 3 or more symptoms (a subset of RSV LRTD with 2 or more symptoms)

The first primary efficacy objective was considered met if the LB of the alpha-adjusted CI of VE was >20% against RSV-LRTD with ≥2 symptoms; the second primary efficacy objective was then subsequently tested against RSV-LRTD with ≥3 symptoms. Success could be declared at an IA when pre-specified total blinded cases had accrued, including when at least 50% of target LRTD cases (defined by both ≥2 and ≥3 symptoms) accrued.

Outcomes/endpoints

The primary endpoints are:

- Numbers and percentages of participants with solicited local and systemic ARs up to 7 days postinjection. Unsolicited AEs up to 28 days postinjection. MAAEs, AESIs, SAEs, and AEs leading to withdrawal up to 24 months postinjection.
- Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days postinjection up to 12 months postinjection.
- Vaccine efficacy of mRNA 1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days postinjection up to 12 months postinjection.

Key-secondary endpoints are:

- Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days postinjection up to 12 months postinjection.
- Vaccine efficacy of mRNA-1345 to prevent first hospitalisation associated with RSV-ARD or RSV-LRTD within the period of 14 days postinjection up to 12 months postinjection.

Sample size

The sample size was driven by the total number of cases required to demonstrate VE (mRNA-1345 vs placebo) to prevent the first episode of RSV-LRTD (primary efficacy endpoints). Based on estimates of RSV-LRTD incidence, up to 37,000 participants were planned to be randomly assigned to receive either 50 µg of mRNA-1345 or placebo using a 1:1 randomisation ratio.

For the first primary efficacy endpoint, the sample size of up to 37,000 participants yielding a total of 86 RSV-LRTD cases with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection in the PPE Set would provide at least 90% power to demonstrate VE (rejecting the null hypothesis H^1_0: VE ≤ 20%). The power calculation was based on the following assumptions using proportional hazards assumption with a log-rank test statistic and a 1-sided type I error rate of 2.5%:

- Randomisation ratio of mRNA-1345 and placebo is 1:1.
- The target VE against RSV-LRTD cases with ≥2 symptoms is 65%.
- The attack rate in the placebo arm for RSV-LRTD cases with ≥2 symptoms is 0.5%.
- Two IAs when at least 50% and 85% of total target RSV-LRTD cases with 2 or more symptoms across the 2 study vaccination groups in the PPE Set, respectively.
- The dropout rate for PPE Set is approximately 10% (not evaluable for the PPE Set).
- Type I error rate will be adjusted using the Pocock boundary for efficacy.
- For the secondary primary efficacy endpoint, the sample size of 37,000 participants and a total of 32 RSV-LRTD cases with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection in the PPE Set would provide approximately 89% power to

demonstrate VE (rejecting the null hypothesis H20: VE ≤ 20%). The power calculation was based on the following assumptions using proportional hazards assumption with a log-rank test statistic and a 1-sided type I error rate of 2.5%:

- The target VE against RSV-LRTD cases with ≥3 symptoms is 80%.
- The attack rate in the placebo arm for the RSV-LRTD cases with ≥3 symptoms is 0.2%.
- Two IAs when at least 50% and 85% of total target RSV-LRTD cases with 3 or more symptoms across the 2 study vaccination groups in the PPE Set, respectively.

The other assumptions were as before.

The nominal 1-sided type I error rate would be 1.55%, 1.18%, and 0.91% at IA1, IA2, and the primary analysis, respectively, if the IAs are conducted exactly at 50% and 85% of total targeted cases for both primary endpoints. Actual alpha to be spent at the IAs would be adjusted based on the actual total case number at the analysis.

For the key secondary efficacy endpoint of VE to prevent the first episode of RSV-ARD, the sample size of 37,000 participants would provide at least 95% power to demonstrate the VE (rejecting the null hypothesis H^3_0: VE ≤ 20%) at a 1-sided alpha level of 2.5%, assuming an attack rate is 2.0% for the first episode of RSV-ARD in the placebo group, and the true VE lies between 50% and 60% (a dropout rate approximately 10% for the PPE Set).

Sample size recalculation

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

Randomisation and blinding (masking)

In both the Phase 2 and Phase 3 segments of the study, assignment to vaccination groups were stratified by age (60 to 74 years versus ≥75 years) and risk factors for LRTD (present versus absent). The study age targeted for enrolment was 60% of participants 60 to 69 years, 30% of participants 70 to 79 years, and 10% of participants ≥80 years. No stratification by region was used.

Risk factors for LRTD were defined as the presence of symptomatic CHF and/or symptomatic COPD at Screening. Symptomatic CHF and COPD diagnosis was defined based on a specific subset of symptoms.

In the Phase 2 and Phase 3 segments of the study, randomisation was conducted in a blinded manner using a centralised IRT and in accordance with pre-generated randomisation schedules. Only the unblinded personnel had controlled access to intervention group assignments. Investigators, study participants, site monitors, and Sponsor personnel (or its designees) were blinded.

An unblinded, external statistical and programming team performed the pre-planned IAs, and an independent DSMB reviewed the unblinded IA results. Once early success was demonstrated at the IA and with DSMB recommendation, the Sponsor unblinded selected Sponsor team members to prepare a CSR to support regulatory submissions. Investigators, study staff, participants, and Sponsor and CRO staff with oversight of study conduct remained blinded to vaccination group allocation for the study duration in order to maintain an observer-blind design.

The safety reviews were to be performed by both a blinded Internal Safety Team (IST) and an independent unblinded DSMB according to a specified monitoring plan outlined in a charter. The IST was to be comprised of members not directly involved in the study. The IST was to conduct ongoing

blinded safety reviews throughout the conduct of the study and was responsible for notifying the DSMB of potential safety signal events.

Statistical methods

Table 3: Analysis sets

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

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

Efficacy analysis was performed using the PPE and mITT Sets. Participants were included in the vaccination group to which they were randomised. The primary analysis population for efficacy was the PPE Set.

Estimands

Four intercurrent events (ICEs) were defined in the SAP (dated 29 Nov 2022):

1) Early discontinuation from study or unrelated death prior to RT-PCR documented RSV-LRTD,
2) RSV-LRTD with start (occurrence) date from Day 1 to Day 14,
3) Use of alternative RSV vaccine, and
4) Use of prohibited medications deemed to impact on efficacy.

Four different estimands were defined (based on two different analyses populations [PPE and mITT set] and two different analysis methods [HR-based and RR-based VE]).

For each of these estimands, different strategies to handling ICEs were defined. These were described by a strategy name only. For ICE 1 and 2 this is always "hypothetical" and for ICE 3 and 4 it is described as "principle stratum" (on the PPE set) or "treatment policy" (on the mITT set).

The primary estimand was Vaccine Efficacy measured as VE (%) = 100% × (1 – HR) in adults ≥ 60 years old who receive IP administration without major protocol deviations impacting efficacy. In detail:

- Target population: Adults aged 60 years or older who receive the IP administration, complete at least 1 visit or surveillance contact 14 days after the IP administration, and have no major protocol deviations impacting the efficacy outcomes.
- Endpoint: First occurrence of protocol-defined RSV-LRTD with event onset within the period of 14 days post-injection up to 12 months post-injection, where the surveillance time is from randomisation up to onset of event, 12 months or censoring
- Treatment conditions: mRNA-1345 (Test) vs. Placebo (Reference)
- Population level summary: Vaccine efficacy defined as 100% × (1-HR) where HR = Hazard Ratio (mRNA-1345 vs. Placebo). The HR is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the vaccination group as a fixed effect, adjusting for stratification factors at randomisation. The time to the first event is calculated as the time (in days) from randomisation to the date of the first event or censoring.
- Intercurrent event strategy: ICE1: Hypothetical; ICE2: Hypothetical; ICE3: Principle Stratum; ICE4: Principle Stratum;

The rationale for the "principle stratum" strategy was: "A principal stratum is used to exclude subjects with major deviations (such as use of alternative vaccines and prohibited medications) so that analysis is a subpopulation composed of participants free from such intercurrent events."

The rationale for the "treatment policy" strategy which was used in a supportive estimand based on the mITT set was: "A treatment policy strategy is used for evaluating vaccine efficacy including all participants vaccinated irrespective of whether they subsequently were found not to strictly meet the key protocol criteria (i.e. major protocol deviations affecting efficacy). There is interest in understanding efficacy in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons."

Handling of Missing Data

Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations, procedures and missing AE dates were defined in the SAP. Other incomplete/missing data were not imputed, unless specified otherwise in the SAP.

Efficacy analyses

Vaccine efficacy (VE) was based on 1 - hazard rate. A stratified Cox proportional hazard model with study vaccination group as a fixed effect, adjusting for stratification factors at randomisation, i.e., age group (≥60 to <75 years or ≥75 years) and risk factors for LRTD (present versus absent), was used to estimate the HR (mRNA-1345 versus placebo). Efron's method was used to handle ties. A multiplicity adjusted 2-sided CI (adjusted for interim analyses, see below) and 95% CI for VE were calculated based on stratified Cox model. After VE was demonstrated, VE and 95% CI were to be provided for subsequent analyses/updates of efficacy.

There were 2 primary efficacy objectives in this study, which were tested in a hierarchical order. Primary efficacy objectives assess efficacy against the first episode of RSV-LRTD starting 14 days post-injection and up to 12 months post-injection (first RSV season). The null hypotheses corresponding to the 2 primary efficacy endpoints were:

- H10: VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥2 symptoms starting 14 days post-injection ≤ 20%, and
- H20: VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥3 symptoms starting 14 days post-injection ≤ 20%.

The study was considered to have met the first and/or second primary efficacy objective if the lower bound of the corresponding 2-sided multiplicity adjusted confidence interval of the VE of mRNA-1345 compared to placebo to prevent RSV-LRTD was >20%.

For the key secondary efficacy objective, the null hypothesis was also tested against the first episode of RSV-ARD starting 14 post-infection and up to 12 months post- injection (first RSV season):

- H30: VE of mRNA-1345 to prevent the first episode of RSV-ARD starting 14 days post-injection ≤ 20%.

The study was considered to have met the key secondary objective if the lower bound of the 2-sided 95% confidence interval of VE of RSV-ARD was > 20% after both primary efficacy endpoints had been met.

Interim analyses

Two IAs were planned for the primary objectives. The first IA was planned to occur when at least 50% of the total cases in the PPE Set were observed for both primary endpoints. The second IA was planned to occur when at least 85% of the total cases in the PP Set were observed for both primary endpoints. The primary analysis was planned to occur when at least 86 RSV-LRTD cases with 2 or more symptoms and at least 32 RSV-LRTD cases with 3 or more symptoms in the PPE Set were observed, respectively.

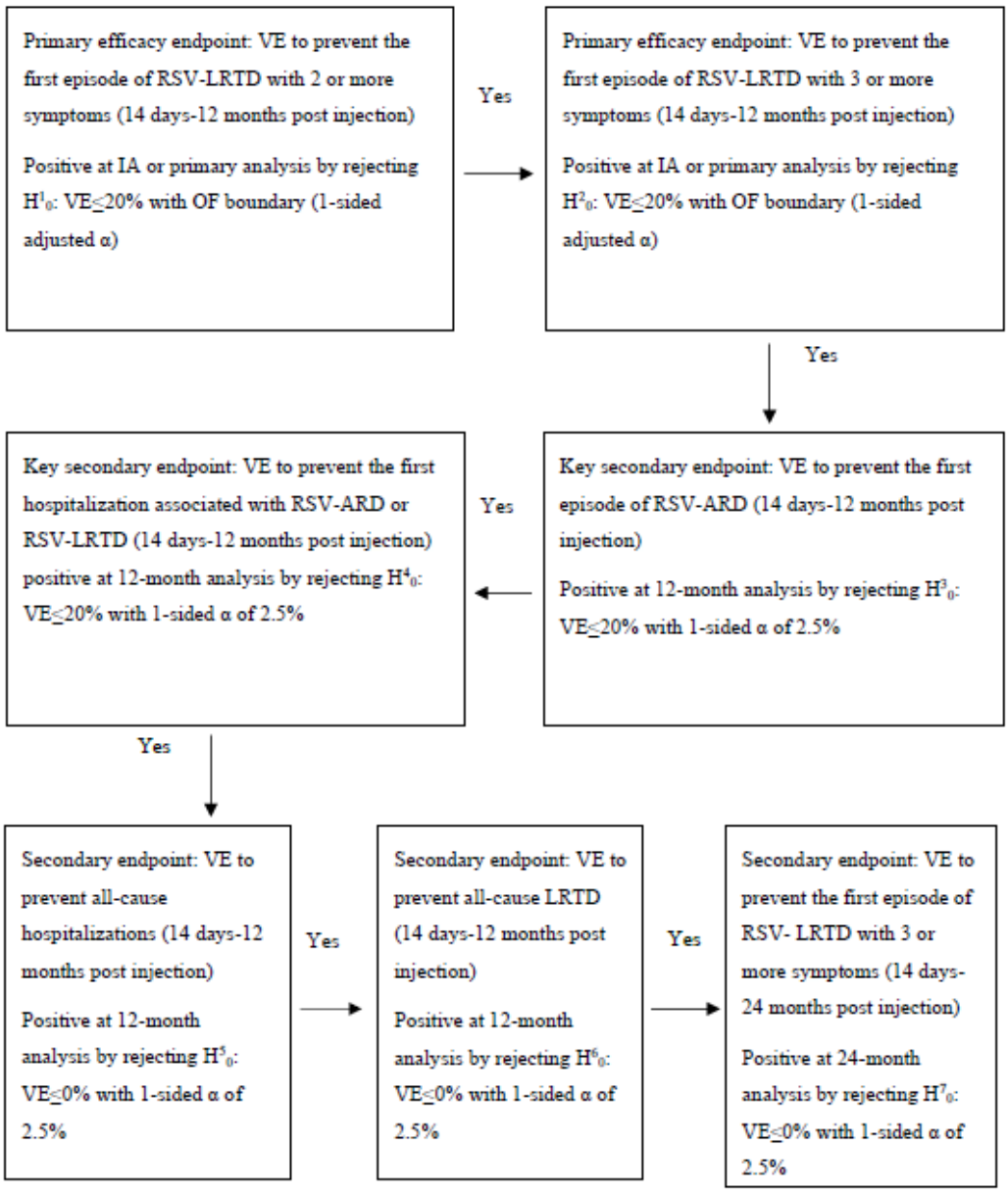
The primary objective of the IAs was for early detection of reliable evidence that the VE was >20%. The Lan-DeMets Pocock approximation alpha-spending function was used for calculating efficacy bounds and to preserve the (1-sided) 2.5% type I error rate over the 2 IAs and the primary analysis. If efficacy was demonstrated for a primary endpoint at an IA, the analysis at this IA was considered as the primary analysis, and any subsequent analysis for this primary endpoint was considered as supportive or supplementary in nature.

The 2 key secondary efficacy endpoints and selected secondary efficacy endpoints were planned to be tested at the planned analysis at Month 12 or final analysis (Month 24), whichever was applicable, if both primary efficacy objectives were met at either of the IAs or primary analysis. At the IA where efficacy was demonstrated for the 2 primary efficacy endpoints, secondary efficacy endpoints could be analysed if the data are available. The final analysis will be performed when all participants have completed Month 24 follow-up.

Multiplicity control over endpoints

In addition to the group sequential design as described above, multiplicity was controlled over the two primary and three key secondary endpoints using a hierarchical testing strategy (see Figure 1). Key secondary endpoints were to be tested at the time of the 12-months analysis or final analysis (after 24 months) as applicable.

Figure 1: Testing sequence of primary and (key) secondary efficacy endpoints (Source: SAP V1.0, 29 Nov 2022); Note that the table still refers to the O'Brien-Fleming spending function (OF) instead of the newly introduced Pocock spending.



Immunogenicity analyses

The secondary immunogenicity endpoints were to be analysed using the PPI Set, by vaccination group, unless otherwise specified. For the immunogenicity endpoints, GM of specific Ab titres with corresponding 95% CI at each timepoint and geometric mean fold rise (GMFR) of specific Ab titres with corresponding 95% CI at each postbaseline timepoint over pre-injection baseline at Day 1 was to be provided by vaccination group.

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

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

Changes to the statistical analyses and study design

Protocol amendment 1 (22 Sept 2022)

The primary analysis method was changed from incidence rate ratio based VE analyses to hazard rate based VE. Negative binomial regression model applied for corresponding updates associated with VE endpoints by incorporating recurrent cases in the analysis.

The interim analysis approach was changed to provide corresponding updates associated with the added primary endpoint for severe cases based on 3+ symptoms.

The power analyses were updated to include the increase in overall sample size and the addition of the second primary endpoint.

Protocol amendment 2 (16 Nov 2022)

The information fraction for performing the first IA was updated to 50% of planned RSV-LRTD cases (43 cases with ≥ 2 symptoms and 16 cases with ≥ 3 symptoms). The information fraction for performing the second IA was updated to 85% of planned RSV-LRTD cases (74 cases ≥ 2 symptoms and 28 cases with ≥ 3 symptoms). The threshold for performing the primary analysis was updated to 86 RSV-LTD cases with ≥ 2 symptoms and 32 RSV-LTD cases with ≥ 3 symptoms. The approximation spending function to preserve the type 1 error rate was changed to Pocock. Adjusted the lower bound for the VE alpha-adjusted CI for primary VE to 20%. All these changes were implemented to harmonise the efficacy success criteria in this study with those of other RSV vaccine candidates in development.

SAP (29 Nov 2022)

Estimand language has been added for primary efficacy endpoints and primary safety endpoints in an appendix.

Table 4: Tabular overview of changes to study design and statistical analyses

	Initial Protocol [07 Oct 2021]	**Amendment 1** [22 Sept 2022]	**Amendment 2** [16 Nov 2022]
Sample size	34,000	37,000	37,000
Analysis method	1 - IRR	1 - HR	1 - HR
First PEP: RSV-LRTD (≥ 2 symptoms)			
Number of targeted events	106	106	86

Power	89% at final analysis	At least 90%	At least 90%
Null hypothesis	H_0: VE ≤ 30%	H_0: VE ≤ 30%	H_0: VE ≤ 20%
Interim analyses	40% (43 cases) 70% (75 cases)	40% (43 cases) 70% (75 cases)	≥ 50% (43 cases) ≥ 85% (74 cases)
Alpha spending function	Undefined; assumed as Lan-DeMets O'Brien-Fleming	Lan-DeMets O'Brien-Fleming	Lan-DeMets Pocock
Nominal significance levels	IA1: 0.04% IA2: 0.73% PA: 2.27%	IA1: 0.04% IA2: 0.73% PA: 2.27%	IA1: 1.55% IA2: 1.18% PA: 0.91%
Second PEP: RSV-LRTD (≥ 3 symptoms)			
Number of targeted events	n.a.	40	32
Power	n.a.	At least 90%	~ 89%
Null hypothesis	n.a.	H_0: VE ≤ 30%	H_0: VE ≤ 20%
Interim analyses	n.a.	40% (16 cases) 70% (28 cases)	≥ 50% (16 cases) ≥ 85% (28 cases)
Alpha spending function	n.a.	Lan-DeMets O'Brien-Fleming	Lan-DeMets Pocock
Nominal one-sided significance levels (as planned)	n.a.	IA1: 0.04% IA2: 0.73% PA: 2.27%	IA1: 1.55% IA2: 1.18% PA: 0.91%

IRR: incidence rate ratio; HR: hazard ratio; PEP: Primary endpoint; RSV-LRTD: RSV-caused lower respiratory tract disease; n.a.: not applicable (as endpoint was only introduced with Amendment 1); IA1: Interim analysis 1; IA2: Interim analysis 2; PA: Primary analysis.

Results

Participant flow

Study mRNA-1345-P301 (referred to as Study P301) is an ongoing Phase 2/3, case-driven, randomised, placebo-controlled, stratified, observer-blind, multicentre study.

Phase 2 was designed to enrol between 400 and 2000 participants to assess safety of the Phase 1-selected vaccine dose prior to full enrolment of the Phase 3 segment.

The full Phase 2/3 study was designed and powered to evaluate mRNA-1345 safety, tolerability, and efficacy against RSV-associated respiratory disease in adults 60 years and older. Data summarised in this CSR are presented and analysed as one dataset for the Phase 2 and Phase 3 segments combined.

Participants in the Phase 2 and in the Phase 3 segments were randomised to receive either 50 µg mRNA-1345 vaccine or placebo in a 1:1 ratio, and assignment was stratified by age (60 to 74 years versus ≥75 years) and presence or absence of CHF and/or COPD as prespecified risk factors for LRTD. These stratifications were implemented to ensure equivalent representation of participants with these risk factors in both vaccine and placebo arms. Enrolment targeted 30% of participants between 70-79 years of age and 10% ≥80 years of age to enrich for groups at higher risk of RSV-LRTD.

The DSMB reviewed Day 29 safety data from more than 400 participants in the Phase 2 segment of P301 (conducted in the US only). Following review of both solicited AR and unsolicited AE data, the DSMB supported seamless advancement to the Phase 3 segment. Study P301 was designed to target a

total of 86 evaluable RSV-LTRD cases with ≥2 symptoms and 32 cases with ≥3 symptoms. Based on RSV disease estimates in older adults, it was estimated that up to 37,000 participants would be enrolled to reach the case targets.

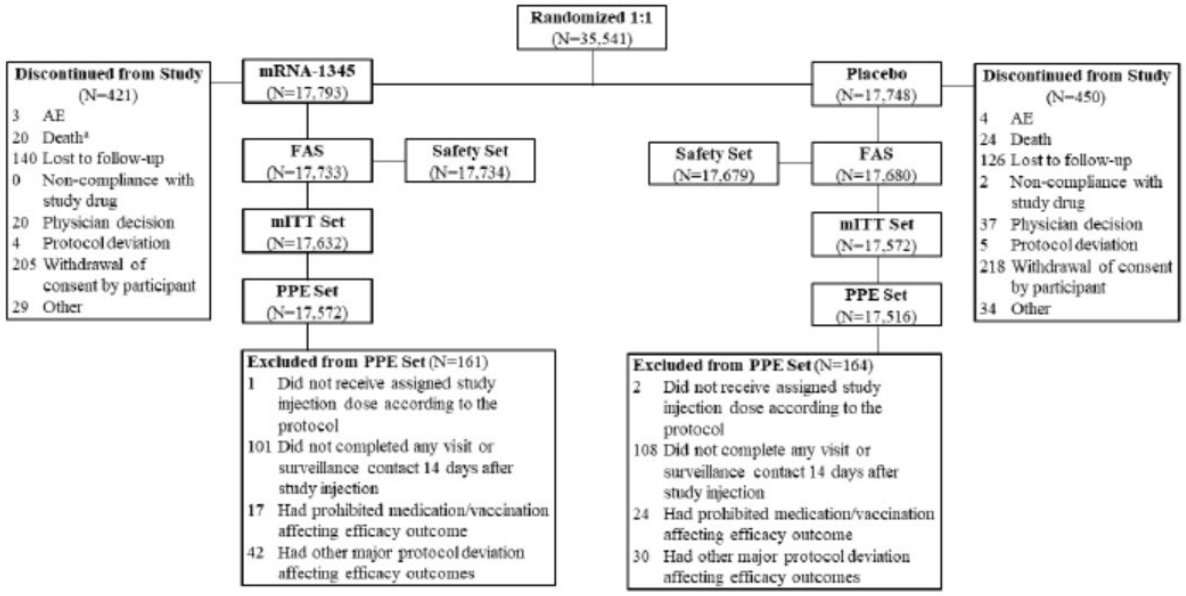
Disposition of Participants

A total of 35,541 participants were randomised to study injection: 17,793 participants in the mRNA 1345 group and 17,748 participants in the placebo group (Figure 2). IP injection was received by 99.7% of the mRNA-1345 group and 99.6% of the placebo group.

At the time of data cutoff (30 Nov 2022), 421 participants (2.4%) in the mRNA-1345 group and 450 participants (2.5%) in the placebo group among the Randomisation Set had discontinued from the study. The most common (≥0.5%) reasons for study discontinuation in both groups were withdrawal of consent by participant and loss to follow-up. The frequencies of reasons for discontinuation were balanced between study groups.

Although most study participants attended sites in the US (54.9%), substantial participation occurred in South America (26.5%), Asia (6.8%), Europe (5.6%), and South Africa (2.8%).

Figure 2: Participant disposition (randomisation set)



Abbreviations: AE = adverse event; CRF = case report form; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PPE = per-protocol efficacy.
The FAS consisted of all randomized participants who received any IP.
The mITT Set consisted of all participants in the FAS who completed at least 1 visit or surveillance 14 days after the IP administration.
The PPE Set consisted of all participants in the mITT Set who received the assigned IP dose according to protocol, completed at least 1 visit or surveillance contact 14 days after the IP administration and had no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.
The Safety Set consisted of all randomized participants who received any IP. Numbers were based on actual treatment group.
[a] Three additional deaths in the mRNA-1345 group were not included here but were included in Table 30, due to data cutoff or missing end-of-study CRF.
Source: Table 14.1.1.1, Table 14.1.2.1, and Table 14.1.2.2.

Recruitment

The time on study, or study duration of follow-up from randomisation, is the time from study injection to discontinuation/completion of study, or data cutoff date (30 Nov 2022), whichever occurred earlier. At the time of the data cutoff, the median study duration after injection was 112 days (range: 1 to 379 days) for both the placebo and the mRNA-1345 groups (Table below).

Most participants (99.5% in each group) had completed ≥28 days of follow-up after injection. In each group, 20.4% had completed ≥6 months of follow-up after injection and 0.2% had completed ≥12 months of follow-up after injection.

Table 5: Summary of study duration (safety set)

	Placebo (N = 17679)	mRNA-1345 50 µg (N = 17734)	Total (N = 35413)
Number of participants, n (%)			
≥7 days since injection	17656 (99.9)	17719 (>99.9)	35375 (99.9)
≥14 days since injection	17637 (99.8)	17694 (99.8)	35331 (99.8)
≥28 days since injection	17584 (99.5)	17649 (99.5)	35233 (99.5)
≥6 months since injection	3607 (20.4)	3609 (20.4)	7216 (20.4)
≥7 months since injection	2413 (13.6)	2422 (13.7)	4835 (13.7
≥8 months since injection	1682 (9.5)	1694 (9.6)	3376 (9.5)
≥9 months since injection	1042 (5.9)	1056 (6.0)	2098 (5.9)
≥10 months since injection	641 (3.6)	656 (3.7)	1297 (3.7)
≥11 months since injection	272 (1.5)	279 (1.6)	551 (1.6)
≥12 months since injection	30 (0.2)	34 (0.2)	64 (0.2)
≥18 months since injection	0	0	0
≥24 months since injection	0	0	0
Number of participants, n (%)			
<7 days since injection	23 (0.1)	15 (<0.1)	38 (0.1)
≥7 days to <14 days since injection	19 (0.1)	25 (0.1)	44 (0.1)
≥14 days to <28 days since injection	53 (0.3)	45 (0.3)	98 (0.3)
≥28 days to <6 months since injection	13977 (79.1)	14040 (79.2)	28017 (79.1)
≥6 months to <12 months since injection	3577 (20.2)	3575 (20.2)	7152 (20.2)
≥12 months to <18 months since injection	30 (0.2)	34 (0.2)	64 (0.2)
≥18 months to <24 months since injection	0	0	0
Study duration from injection (days)			
n	17679	17734	35413

Conduct of the study

The protocol was finalised on 07 Oct 2021 and amended twice, on 22 Sept 2022 and 16 Nov 2022.

Amendment 1 implemented RSV-LRTD with 3 or more symptoms as additional primary endpoint to be tested after RSV-LRTD with 2 or more symptoms has met its objective. The sample size was increased from ~ 34.000 to 37.000 subjects in order to provide adequate power for the second primary endpoint (RSV-LRTD with ≥ 3 symptoms). The futility analysis was removed because study enrolment would have been nearly complete when the DSMB reviewed the futility analysis results.

Amendment 2 was implemented to harmonise the prespecified efficacy statistical success criteria with the published criteria, through an updated IA success criterion of a lower bound of the alpha-adjusted

CI of VE >20%. Alpha spending approach was updated from a Lan-DeMets O'Brien-Fleming approach to a Lan-DeMets Pocock approximation function.

Baseline data

The demographics are overall well balanced between the mRNA-1345 group and placebo group.

Numbers analysed

The primary objective was analysed against a total of 64 cases out of 35,088 participants that met the case definition of RSV-LRTD with ≥2 symptoms. Within this total of 64 cases, a subset of 20 cases met the case definition of RSV-LRTD with ≥3 symptoms.

Outcomes and estimation

Vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms, and VE of 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms was demonstrated in the initial IA. Therefore, the primary objectives according to the latest protocol version were met.

The number of person years in each analysis were comparable between the mRNA-1345 group and the placebo group, indicating a comparable rate of enrolment and drop-out between these groups.

Sensitivity analyses were conducted based on actual strata, using the mITT Set and using the expanded case definition. In these sensitivity analyses no changes in case totals or case split was observed. An analysis that excluded cases of co-infection with other pathogens demonstrated a VE of 84.1% (95% CI: 66.4, 92,4) against RSV-LRTD with ≥2 symptoms, and VE of 81.3% (95% CI: 35.8, 94.6) against RSV-LRTD with ≥3 symptoms.

The Cumulative Incidence Curves for first episode of RSV-LRTD (with 2 or more symptoms or 3 or more symptoms) between 14 days post-injection up to 12 months post-injection show a cumulative increase of cases in the placebo group while the number of cases in the mRNA-1345 group remains at a lower level of cases over time. However, the numbers of the patients at risk are dramatically decreasing after 3 months of follow-up (from 17 516 in the beginning (placebo group) to 7 866 (44.9%) after 4 months, 5 314 (30.3%) after 5 months, 3 657 (20.9%) after 6 months, 2 304 (13.2%) after 7 months, 1 602 (9.1%) after 8 months, 1 050 (6%) after 9 months, 629 (3.6%) after 10 months, 267 (1.5%) after 11 months and 43 (0.2%) after 12 months. The decrease of numbers of patients at risk is comparable between the mRNA-1345 group and the placebo group, indicating comparable enrolment and censoring in both groups. There is however a substantial portion (>50%) with only 3 months or less follow-up time. This does not cover even a single RSV season. More mature data was needed to allow a good assessment of the duration of protection and potential subgroup differences. Therefore, the applicant was asked to provide more recent results with a later data cut-off and longer follow-up time. A careful discussion on regional differences triggered e.g., by different enrolment times and/or different attack rates was requested to be included in addition. The applicant provided an analysis with a cutoff date of 30 Apr 2023. The Additional Analysis of Efficacy – encompassing cumulative cases accrued through 30 Apr 2023 and after the RSV season had peaked in the US – had numerically lower VE point estimates than those assessed in the Primary Analysis (30 Nov 2022 data cutoff date). However, VE CIs were overlapping with the Primary Analysis and the LB of the 95% CI was >20% for all endpoints. The PPE dataset for the Additional Analysis of Efficacy included a total of 36 157 participants, followed for a median of 8.6 months (range 1-530 days). In the Additional Analysis of Efficacy, 271 total cases of RSV-ARD, 174 total cases of RSV LRTD with ≥2 symptoms, and 70 cases of RSV-LRTD with ≥3 symptoms accrued. Against RSV-LRTD with ≥2 symptoms, VE was 63.3% (95% CI: 48.7, 73.7), and against RSV-LRTD with ≥3 symptoms, VE was

63.0% (95% CI: 37.3,78.2). VE against RSV-ARD was 53.9% (95% CI: 40.5, 64.3), which does not exclude cases of RSV-LRTD.

In the initial IA the cases of RSV-LRTD with ≥2 symptoms the rates of the symptoms reported are higher in the placebo group for fever (placebo vs. mRNA-1345: 23.6% vs. 0%), tachypnoea (3.6% vs. 0%), and hypoxemia (1.8% vs. 0%) and pneumonia (1 case vs 0 cases) compared to the mRNA-1345 group. In the cases of RSV-LRTD with ≥3 symptoms the rates of the symptoms reported in the placebo group are higher for shortness of breath (70.6% vs. 33.3%), fever (35.3% vs. 0%), tachypnoea (11.8% vs. 0%), and hypoxemia (5.9% vs. 0%) and pneumonia (1 case vs. 0 cases) compared to the mRNA-1345 group.

Sub-group analyses were conducted on strata such as age, sex, race, ethnicity, region, co-morbid conditions and other risk factors. These sub-groups had variable numbers of events making analysis difficult. There was no tendency of lower VE in older sub-groups (although LB of CI in Age Group 1; ≥75 years was in the negative due to low numbers of participants and cases). VE in male and female is comparable (84.1%, 83.4%). For participants with risk factors such as COPD/CHF the VE drops to 49.4% (CI: -457.9, 95.4) which is at least impacted by low numbers of participants (1217 and 1207, respectively) and low numbers of events (2 cases placebo group vs. 1 case mRNA-1345 group). Overall, VE values for the sub-groups are in the range as for the PPE analysis.

Ancillary analyses

The applicant provided a VE of 68.4% (95% CI: 50.9, 79.7) against RSV-ARD in the initial interim analysis study report and claimed protection against RSV-ARD after vaccination with mRNA-1345. It is noted that the assessment of RSV-ARD was not planned until the 12 months analysis. No interim analysis was specified, which would justify the analysis of these data at an earlier time point. Data-driven choices cannot be excluded and no type 1 error control exists for this analysis. As RSV-LRTD cases are included in RSV-ARD cases it is not clear how far RSV-LRTD cases are driving the estimated VE for RSV-ARD. As the prevention of ARD is broader than the prevention of LRTD the applicant was asked to additionally provide VE results on RSV-ARD cases only, i.e. excluding all LRTD cases, and to discuss the clinical relevance of these results.

The applicant provided an analysis of RSV-ARD without RSV-LRTD cases calculated from results of the initial IA as below:

table 6: Vaccine efficacy of mrna-1345 against first episode of rsv-ard starting 14 days after vaccination, excluding cases of rsv-lrtd with ≥2 symptoms, ppe set, study mrna-1345-p301 (data cutoff 30nov2022)

Endpoint	**mRNA-1345 N=17572 Cases n (%)**	**Placebo N=17516 Cases n (%)**	**VE[a], % (95% CI)[b]**
First episode of RSV-ARD	17 (0.10)	27 (0.15)	37.3 (-15.1, 65.8)

The VE against RSV-ARD only cases is 37.3% (95% CI: -15.1, 65.8) with the LB of the CI crossing the zero.

Considering the medical purpose of this vaccine as well as the severity and clinical relevance of the different clinical manifestations of RSV disease ARD was requested to be removed from the indication

statement (Section 4.1 of the SmPC). The applicant agreed in the response to remove ARD from the indication in the SmPC (section 4.1).

The applicant was also requested to remove results against RSV-ARD from section 5.1 of the SmPC. In D180 responses the applicant confirmed that ARD has been removed from the SmPC section 5.1 and the revised Product Information has been provided within the response package.

In the initial IA the applicant demonstrated a VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥2 symptoms of 91.7% (95% CI: 73.0%, 97.4%) against RSV-A and 68.5% (95%CI: 21.1%, 87.4%) against RSV-B. VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥3 symptoms was 90.0% (95% CI: 22.0%, 98.7%) against RSV-A and 71.5% (95% CI: −37.0%, 94.1%) against RSV-B. The LB of the CI for VE against RSV-B crosses the zero which is impacted by the low number of cases. Formally, protection against a first episode of RSV-LRTD with ≥3 symptoms due to infection with RSV-B was not demonstrated. The VE against RSV-B is lower compared to RSV-A although the F-protein is conserved between these RSV sub-types. The applicant was asked to discuss this observation.

The applicant responded that the subgroup analyses were not intended for formal statistical inference and the study was hence not powered to show protection against each specific subtype, which is agreed.

However, it is observed that the VE against RSV-B is lower compared to RSV-A. This is accompanied by, and probably a result of lower nAB titres against RSV-B as compared to RSV-A, as provided with the mRNA-1345-P301 Global Immunogenicity Analysis Report.

The applicant further responded that in order to assess whether the observation has any clinical impact, cases of RSV-LRTD (with ≥2 and ≥3 symptoms) caused by RSV-B were assessed for clinical presentation. The applicant summarises that results show that breakthrough cases in the mRNA-1345 group were not more severe than cases in the placebo group. While this is agreed, it was not expected that breakthrough cases result in increased severity of RSV-B mediated disease.

The applicant has therefore not responded regarding the implications of lower immune responses and efficacy against RSV-B compared to RSV-A. Instead, the applicant has addressed potential differences in severity of the breakthrough cases between RSV-A and RSV-B. As these subgroups are based on intercurrent events (i.e. post-baseline events which cannot be influenced by e.g. excluding a specific population from the label), this issue will not be further pursued.

It is noted that the protective effect against RSV-B after vaccination with mRNA-1345 is lower as compared to a protective effect against RSV-A. This might be a result from the fact that the sequence of RSV-A Pre-F protein from RSV-A is used in the vaccine mRNA-1345.

Summary of main efficacy results

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 7: Summary of efficacy for trial mRNA-1345-P301

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age			
Study identifier	Study Number: mRNA-1345-P301 EudraCT Number: 2021-005026-20 Investigational New Drug Number: 23342 NCT05127434 IRAS ID: 1004704		
Design	Seamless phase 2/3 study design; Observer-blind; placebo-controlled; covering up to 12 months (17 Nov 2021 (FPFV) – 30 Nov 2022 (data cut-off)) with 1.5 RSV seasons; Interim Analysis		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		up to 12 months not applicable not applicable; ongoing
Hypothesis	Efficacy		
Treatments groups	mRNA-1345		17 793 participants, mRNA-1345
	Placebo		17 748 participants, placebo
Endpoints and definitions	Co-Primary endpoint	VE measured against the first occurrence of RSV-LRTD with 2 or more symptoms VE measured against the first occurrence of RSV-LRTD with 3 or more symptoms	• Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days postinjection up to 12 months postinjection. • Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days postinjection up to 12 months postinjection.
	Key Secondary endpoint	VE measured against the first occurrence of RSV-ARD	Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days postinjection up to 12 months postinjection.

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age			
Study identifier	Study Number: mRNA-1345-P301 EudraCT Number: 2021-005026-20 Investigational New Drug Number: 23342 NCT05127434 IRAS ID: 1004704		
	Key Secondary endpoint	VE measured against the first hospitalisation associated with RSV-ARD or RSV-LRTD	Vaccine efficacy of mRNA-1345 to prevent first hospitalisation associated with RSV-ARD or RSV-LRTD within the period of 14 days postinjection up to 12 months postinjection.
Database lock	25 Jan 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per Protocol Efficacy, Interim Analysis 1		
Descriptive statistics and estimate variability	Treatment group	Placebo	mRNA-1345
	Number of subject	17 516	17 572
	Events of RSV-**LRTD with 2** or more symptoms (%)	55 (0.31%)	9 (0.05%)
	Events of RSV-**LRTD with 3** or more symptoms (%)	17 (0.10)	3 (0.02%)
	Events of RSV-**ARD** (%)	82 (0.47%)	26 (0.15%)
Effect estimate per comparison	Co-Primary endpoint: RSV-**LRTD with 2** or more symptoms	Placebo	mRNA-1345
		VE based on HR (%)	83.7
		Alpha-adjusted 95.88% CI	66.0, 92.2
		P-value	<0.0001

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age			
Study identifier	Study Number: mRNA-1345-P301 EudraCT Number: 2021-005026-20 Investigational New Drug Number: 23342 NCT05127434 IRAS ID: 1004704		
	Co-Primary endpoint: RSV-**LRTD with 3** or more symptoms	Placebo	mRNA-1345
		VE based on HR (%)	82.4
		Alpha-adjusted 96.36% CI	34.8, 95.3
		P-value	<0.0078
	Key-Secondary endpoint: RSV-**ARD**	Placebo	mRNA-1345
		VE based on HR (%)	68.4
		95% CI	50.9, 79.7
		P-value	not available
Notes	The applicant was requested to remove RSV-ARD results from the indication statement (Section 4.1 of the SmPC) and efficacy description in section 5.1.		

Results and Analysis			
Analysis description	**Additional Analysis of Efficacy (data cutoff 30 Apr 2023)**		
Analysis population and time point description	Per Protocol Efficacy, Interim Analysis 1		
Descriptive statistics and estimate variability	Treatment group	Placebo	mRNA-1345
	Number of subjects	18 045	18 112

	Events of RSV-**LRTD with 2** or more symptoms (%)	127 (0.70%)	47 (0.26%)
	Events of RSV-**LRTD with 3** or more symptoms (%)	51 (0.28)	19 (0.10%)
	Events of RSV-**ARD** (%)	185 (1.03%)	86 (0.47%)
Effect estimate per comparison	Co-Primary endpoint: RSV-**LRTD with 2** or more symptoms	Placebo	mRNA-1345
		VE based on HR (%)	63.3
		Alpha-adjusted 95.88% CI	48.7, 73.7
	Co-Primary endpoint: RSV-**LRTD with 3** or more symptoms	Placebo	mRNA-1345
		VE based on HR (%)	63.0
		Alpha-adjusted 96.36% CI	37.3, 78.2
	Key-Secondary endpoint: RSV-**ARD**	Placebo	mRNA-1345
		VE based on HR (%)	53.9
		95% CI	40.5, 64.3

Immunogenicity clinical study mRNA-1345-P301

In the applicant's Day 120 response immunogenicity data for Study P301 have been submitted.

Objectives and endpoints

Immunogenicity objectives and endpoints for Study P301 are shown in the Table below. This report summarises nAb and bAb responses measured from placebo and mRNA-1345 recipients at Baseline and Day 29, including results on the Ab responses obtained on Day 15 (from participants in the Phase 2 segment of Study P301); additional timepoints will be analysed and provided in the frame of a recommendation.

Table 8: Immunogenicity objectives and endpoints

Objectives	Endpoints
• The immunogenicity objective is to evaluate the response to a single dose of mRNA-1345 vaccine from Baseline up to 24 months postinjection.	• GMT of serum RSV nAbs and GMC of serum RSV bAbs at Baseline (Day 1), Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546, and Day 730. • SRR of serum RSV nAbs and bAbs at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546, and Day 730. Seroresponse for RSV nAbs is defined as: – a postinjection titer ≥4 x LLOQ if Baseline is <LLOQ OR – a ≥4-fold increase from Baseline in postinjection titers if Baseline is ≥LLOQ. • GMFR of postinjection/Baseline titers for RSV nAbs and bAbs at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546, and Day 730. • Proportion of participants with ≥2-fold increases in RSV nAb titers and bAb concentration at Day 15 (in Phase 2 only), Day 29, Day 181, Day 365, Day 546, and Day 730.

Abbreviations: bAb = binding antibody; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; nAb = neutralising antibody; RSV = respiratory syncytial virus; SRR = seroresponse rate.

Immunogenicity Assays

• Microneutralisation Assay: Serum nAb titres against RSV-A and RSV-B were measured using validated microneutralisation assays, which quantitatively measured the nAbs against RSV-A and RSV-B. Results are expressed as (i) absolute titres and as (ii) IU/mL. Conversion of nAb titres to IU/mL was performed by multiplying the sample's absolute titre by 1.0578 for RSV-A or 0.6936 for RSV-B, as per the international standard antiserum to RSV-A and RSV-B from the World Health Organization (2020).

• Binding Antibody Assay: Serum bAb against RSV preF and RSV postF antigens were measured using a validated quantitative multiplex assay. The assay was based on Luminex® technology that quantitatively measures the IgG antibodies to RSV preF and postF. The measured signal was directly proportional to the amount of antigen specific serum IgG antibodies present in the serum samples. Results are expressed in AU/mL.

Immunogenicity Assessments

Serum samples for immunogenicity assessments were collected at prespecified timepoints: Baseline (Day 1), Day 15 (Phase 2 segment only), Day 29, Day 181, Day 365, Day 546, and Day 730. This report summarises results obtained at Baseline and Day 29; data from the remaining timepoints will be analysed at a future date.

Disposition

A total of 1922 participants were included in the Random Immunogenicity Subcohort, of these 74 participants (3.9%) were excluded from the PPI Set, leaving a total of 1848 participants (96.1%) in the PPI Set. The most common reason for exclusion from the PPI Set was that the participant did not have a valid immunogenicity level result after IP administration (68 participants [3.5%]).

Table 9: Reasons for exclusion from ppi set

	Placebo (N=351)	mRNA-1345 50 µg (N=1571)	Total (N=1922)
Random Immunogenicity Subcohort	351	1571	1922
Per-Protocol Immunogenicity Set, n (%)	333 (94.9)	1515 (96.4)	1848 (96.1)
Excluded from Per-Protocol Immunogenicity Set, n (%)	18 (5.1)	56 (3.6)	74 (3.9)
Reasons for exclusion, n (%)[a]			
Did not receive sssigned IP dose according to protocol	0	0	0
Did not have a valid immunogenicity level result before IP administration[b]	0	2 (0.1)	2 (0.1)
Did not have a valid immunogenicity level result after IP administration	17 (4.8)	51 (3.2)	68 (3.5)
Had prohibited medication/vaccination affecting immunogenicity outcomes	0	0	0
Had other major protocol deviations affecting primary immunogenicity outcomes	1 (0.3)	3 (0.2)	4 (0.2)

Abbreviations: IP = investigational product; PPI = Per-Protocol Immunogenicity Set.

Percentages were based on the number of participants in the Random Immunogenicity Subcohort.

a. A participant who had multiple reasons was counted only once based on the order of the reasons for exclusion listed.

b. In this context, the term "valid" means that a titre or concentration value was reported by the laboratory.

Demographics

The total PPI Set had a mean age of participants of 72.1 years and 54.9% were male, 77.9% White, 52.7% not Hispanic or Latino, and 56.1% were from high-income countries. The PPI Set was stratified for participants between 60 to 74 years and those ≥75 years, between those with and without LRTD risk factors, and those from Northern and Southern Hemisphere. The total PPI Set included 45.7% of participants with ≥75 years, 39.8% participants with an RSV-LRTD risk factor, 56.4% participants from the Northern Hemisphere, and 43.6% from the Southern Hemisphere. Further, the PPI Set included 19.9% participants who identified as vulnerable/frail based on the Edmonton Frailty Score.

Details are presented in the table below:

Table 10: Baseline demographics and characteristics (ppi set)

	Placebo (N=333)	mRNA-1345 50 µg (N=1515)	Total (N=1848)
Age at enrollment (years)			
n	333	1515	1848
Mean (SD)	72.9 (7.36)	71.9 (7.31)	72.1 (7.33)
Median	74.0	72.0	73.0
Min, max	60, 94	60, 94	60, 94
Age Group 1, n (%)[a]			
60 to 74 years	168 (50.5)	836 (55.2)	1004 (54.3)
≥75 years	165 (49.5)	679 (44.8)	844 (45.7)
Age Group 2, n (%)[a]			
60 to 69 years	120 (36.0)	619 (40.9)	739 (40.0)
70 to 79 years	154 (46.2)	673 (44.4)	827 (44.8)
≥80 years	59 (17.7)	223 (14.7)	282 (15.3)
LRTD risk factors (CHF/COPD), n (%)[a]			
Present	150 (45.0)	585 (38.6)	735 (39.8)
CHF	35 (10.5)	110 (7.3)	145 (7.8)
COPD	108 (32.4)	444 (29.3)	552 (29.9)
CHF and COPD	7 (2.1)	31 (2.0)	38 (2.1)
Absent	183 (55.0)	930 (61.4)	1113 (60.2)
Gender, n (%)			
Male	182 (54.7)	833 (55.0)	1015 (54.9)
Female	151 (45.3)	682 (45.0)	833 (45.1)
Race group, n (%)			
White	267 (80.2)	1172 (77.4)	1439 (77.9)
Black	27 (8.1)	133 (8.8)	160 (8.7)
Asian	12 (3.6)	66 (4.4)	78 (4.2)
Other[b]	26 (7.8)	141 (9.3)	167 (9.0)
Unknown/not reported	1 (0.3)	3 (0.2)	4 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	147 (44.1)	705 (46.5)	852 (46.1)
Not Hispanic or Latino	184 (55.3)	789 (52.1)	973 (52.7)
Unknown	0	3 (0.2)	3 (0.2)
Not reported	2 (0.6)	18 (1.2)	20 (1.1)
Frailty status 1, n (%)			
0-3: Fit	235 (70.6)	1034 (68.3)	1269 (68.7)
4-5: Vulnerable	58 (17.4)	310 (20.5)	368 (19.9)
6 or More: Frail	36 (10.8)	149 (9.8)	185 (10.0)
Missing	4 (1.2)	22 (1.5)	26 (1.4)
Region			
Northern Hemisphere	195 (58.6)	848 (56.0)	1043 (56.4)
Southern Hemisphere	138 (41.4)	667 (44.0)	805 (43.6)
World Bank Region, n (%)			
North America/Europe	163 (48.9)	686 (45.3)	849 (45.9)
Central/Latin America/Africa	146 (43.8)	721 (47.6)	867 (46.9)
Asia Pacific	24 (7.2)	108 (7.1)	132 (7.1)
World Bank income level 2022, n (%)			
Lower-middle-income economies	6 (1.8)	34 (2.2)	40 (2.2)
Upper-middle-income economies	125 (37.5)	646 (42.6)	771 (41.7)
High-income countries	202 (60.7)	835 (55.1)	1037 (56.1)

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; eCRF = electronic case report form; LRTD = lower respiratory tract disease; max = maximum; min = minimum; PPI = Per-Protocol Immunogenicity Set; SD = standard deviation

Percentages were based on the number of participants in the Per-Protocol Immunogenicity Set.

a. Derived from age and risk collected on eCRFs.

b. Other races included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple.

Table 11: Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	Study P301 enrolled elderly subjects 60 years of age and older.		
Non Controlled trials	N/A	N/A	N/A

RSV infection is relevant to young children and elderly subjects. The current application claims an indication in elderly subjects ≥60 years of age.

2.6.5.3. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.5. Supportive study(ies)

The supportive studies, **mRNA-1345-P101** and **mRNA-CRID-001**, both evaluated immunogenicity of mRNA-1345. No efficacy results were obtained.

1. **Study mRNA-1345-P101**

Study mRNA-1345-P101 is a phase 1, randomised, observer-blind, placebo-controlled, dose escalation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus (RSV), in healthy younger adults aged 18 to 49 years, women of child-bearing potential aged 18 to 40 years, healthy older adults aged 65 to 79 years, Japanese older adults aged ≥60 years, and RSV-seropositive children aged 12 to 59 months.

Study P101 data also resulted in the selection of an mRNA-1345 dose level and vaccination schedule for subsequent clinical development in adults.

Methods:

Study participants:

Up to 651 eligible participants will be randomly assigned and dosed in this study including 100 younger adult participants 18 to 49 years of age in 4 cohorts (Cohorts 1, 2, 3, and 4), 180 women of child-

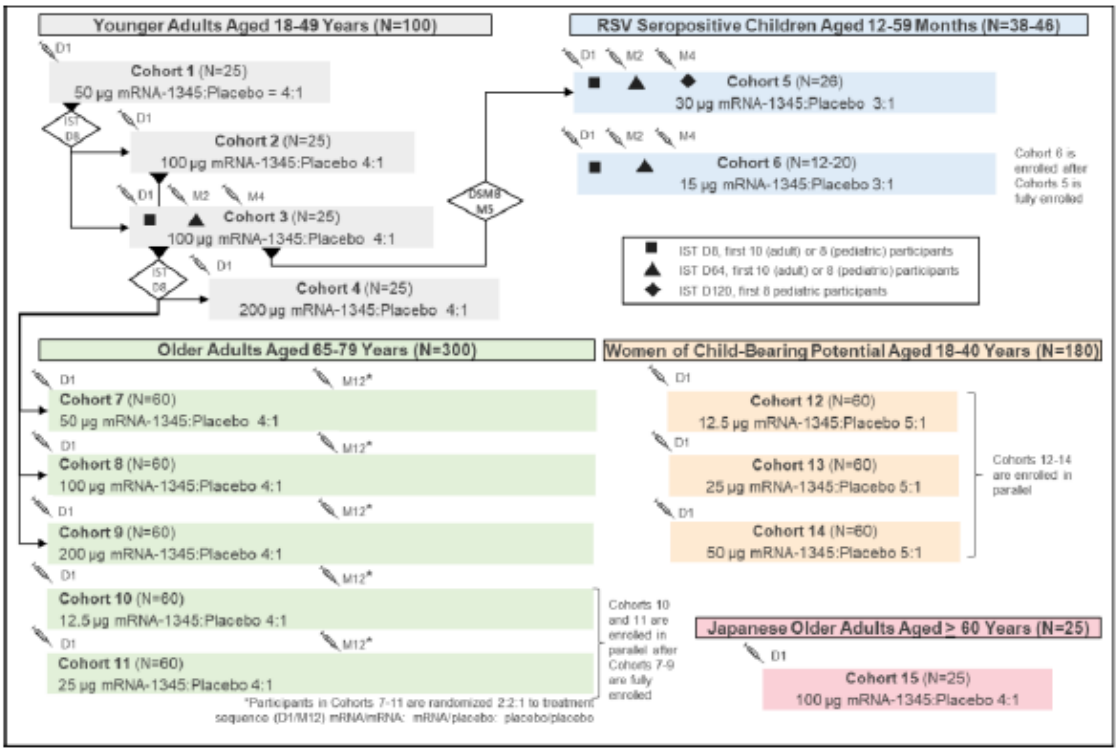
bearing potential participants 18 to 40 years of age in 3 cohorts (Cohorts 12, 13, and 14), 300 older adult participants 65 to 79 years of age in 5 cohorts (Cohorts 7, 8, 9, 10, and 11), 25 Japanese older adult participants ≥ 60 years of age in 1 cohort (Cohort 15), and up to 46 RSV-seropositive children 12 to 59 months of age in 2 cohorts (Cohorts 5 and 6).

Study P101 was carried out in USA (conducted at 21 clinical sites in the US).

Study design

Phase I, randomised, observer-blind, placebo-controlled, dose escalation study. The study was conducted with the oversight of both an IST and an independent, external DSMB.

Figure 3: Study design overview



Abbreviations: D = Day; DSMB = Data Safety Monitoring Board; IST = Internal Safety Team; M = Month; mRNA = messenger RNA; RSV = respiratory syncytial virus. Note: Only data from adult participants in Cohorts 1 to 4 (Final analysis), 7 to 11 (Interim analysis), and 15 (Final analysis) were evaluated in this report.

Main Criteria for Inclusion and Exclusion:

Healthy individuals within the specified populations were eligible to participate if they did not have medical conditions or medication requirements that could affect immunogenicity assessments or that might represent a safety concern (such as history of anaphylactic reaction following a vaccination, poorly controlled hypertension, or significant chronic pulmonary or cardiovascular disease).

- **Treatments**

Participants received either a selected dose of mRNA-1345 or a dose of Placebo (0.9% sodium chloride) via intramuscular injection (IM) in the deltoid muscle.

The study interventions and arm assignments are outlined in the below ***Table 12***.

Table 12: Summary of treatment for cohorts assigned

Cohorts	mRNA-1345 Dose	Injections	mRNA-1345 N	Placebo N
Healthy adult participants 18 to 49 years of age[a]				
Cohort 1	50 µg	1	20	5
Cohort 2	100 µg	1	20	5
Cohort 3	100 µg	3	20	5
Cohort 4	200 µg	1	20	5
Total	-		80	20
Healthy adult participants 65 to 79 years of age[b,c]				
Cohort 7	50 µg	2	48	12
Cohort 8	100 µg	2	48	12
Cohort 9	200 µg	2	48	12
Cohort 10	12.5 µg	2	48	12
Cohort 11	25 µg	2	48	12
Total	-		240	60
Healthy adult participants of Japanese descent aged ≥60 years				
Cohort 15	100 µg	1	20	5
Total	-		20	5

All participants received a first injection on Day 1. Participants assigned to Cohort 3 received the second injection on Day 57 and the third injection on Day 113.

b. All participants received 1 injection on Day 1 and a booster injection (Dose 2) approximately 12 months later. For Dose 2, participants who received mRNA-1345 for Dose 1 were randomised to receive either mRNA-1345 or placebo, and participants who received placebo for Dose 1 received placebo. They were randomised based on the randomisation ratio 2:2:1 to the following treatment sequences (Day 1/Month 12): mRNA-1345/mRNA-1345: mRNA-1345/placebo: placebo/placebo.

c. Cohorts 7, 8, and 9 were enrolled in parallel. Cohorts 10 and 11 were enrolled in parallel after Cohorts 7, 8, and 9 were fully enrolled.

Sample size

There was no hypothesis testing in this study. The sample size was regarded as sufficient to provide descriptive summary of the tolerability and immunogenicity of different dose levels of mRNA-1345.

For the older adult cohorts, a sample size of 240 participants receiving mRNA-1345 has at least a 95% probability to observe at least 1 participant with an AE at a true 1.24% AE rate.

Randomisation

The cohorts of healthy adults 18 to 49 years of age and healthy adults of Japanese descent ≥60 years of age were randomised (in a 4:1 ratio within each dose level cohort) to receive mRNA-1345 or placebo and did not receive a booster injection at Month 12. The cohorts of healthy adults 65 to 79 years of age were randomised (in a 2:2:1 ratio within each dose level cohort) to receive mRNA-1345/mRNA-1345, mRNA-1345/placebo, or placebo/placebo for the initial/Month 12 booster injections.

Blinding

The study was observer-blind, such that only designated unblinded study personnel responsible for vaccine preparation, administration, and/or accountability had access to study treatment assignments.

Statistical methods for immunogenicity analyses

The following evaluations for immunogenicity analyses are presented:

- The GMTs of serum RSV-A and RSV-B nAbs with 95% CI at each immunogenicity visit. The 95% CI was calculated based on the t-distribution of the log-transformed values for GMT then back transformed to the original scale. The GMTs are also expressed in IU/mL as per WHO international standards.
- The GMCs for RSV PreF and PostF-bAbs with 95% CI at each immunogenicity visit. The 95% CI was calculated based on the t-distribution of the log-transformed values for GMC then back transformed to the original scale. The GMCs are expressed as AU/mL.
- The GMFRs of postbaseline/baseline antibody titres with 95% CI at each individual postinjection time point over baseline. The 95% CIs were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale. The GMFR of GMT or GMC with corresponding 95% CI at a postbaseline visit over baseline were also to be provided.
- Number and percentage of participants with ≥2-fold and ≥4-fold increases in titres from baseline at each postinjection time point. The two-sided exact 95% CI was calculated using the Clopper-Pearson method.

Results

Participants flow

Participants were randomised and received the vaccine according to the cohorts/age groups as follows:

Adults Aged 18 to 49 years:

Single injection: a total of 75 participants aged 18 to 49 years received a single injection of 50 µg, 100 µg, or 200 µg mRNA-1345 (n=20 participants per group) or placebo (n=15);

3 injections: a total of 25 participants aged 18 to 49 years received 3 injections of 100 µg mRNA-1345 (n=20) or placebo (n=5). In the mRNA-1345 group, all participants received the first injection, 16/20 participants (80.0%) received the second injection, and 15/20 participants (75.0%) received the third injection.

Adults Aged 65 to 79 years:

First injection: a total of 298 participants aged 65 to 79 received a first injection of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg mRNA-1345 (47 to 48 participants per group) or placebo (n=59).

A total of 11.7% of participants in the placebo group and 17.1% of participants in the mRNA-1345 groups discontinued study vaccination after the first injection and before booster injection. The most common reasons for discontinuation of vaccination were withdrawal of consent and LTFU.

Booster injection: Among the 298 participants aged 65 to 79 years who received a first injection of mRNA-1345 or placebo, 247 participants received a booster injection; 52 participants in the placebo/placebo group, 96 participants in the mRNA-1345/placebo groups, and 99 participants in the mRNA-1345/mRNA-1345 groups.

Adults of Japanese Descent Aged ≥60 Year: a total of 25 adults of Japanese descent aged ≥60 years received 1 injection of 100 µg mRNA-1345 (n=20) or placebo (n=5), and all participants completed the study.

Recruitment

The initiation (first participant first visit) up to data cutoff date in Study P101, according to the cohorts and age groups was done as following:

Cohorts:

- 1 to 4 Adults aged 18 to 49 years: 22 Sep 2020 to 27 Sep 2021 (Final analysis)
- 7 to 11 Adults aged 65 to 79 years: 28 Jan 2021- 03 Oct 2022 (Month 14) (Interim analysis)
- 15 Adults of Japanese descent aged ≥60 years :18 Nov 2021-13 Sep 2022 (Final analysis)

The database lock date of 06 Feb 2023.

Conduct of the study

The protocol was amended 8 times over a 2 years' time period. Protocol version 8.0 was valid on 01st June 2022. The current Interim CSR is dated 14 April 2023. All protocol versions have been provided together with an overview of the major protocol changes.

Baseline data

In Study P101 baseline demographics results were generally well balanced across the 5 groups receiving various dose levels of vaccine. Participants were generally White, non-Hispanic and were all healthy adults. Among the 47 participants 65 to 79 years of age who received at least 1 dose of 50 µg mRNA-1345, the median age was 69.0 years (range: 65 to 78 years), 52.1% of participants were female, 93.8% of participants were White, and 93.8% of participants were not Hispanic or Latino. All Study P101 participants were from the United States.

Immunogenicity Assessments

Blood samples for antibody-mediated immunogenicity assessments were collected at the time points indicated for each age group participants.

Per-Protocol Set

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the treatment arm to which they are randomised.

Outcomes and Estimations

Secondary Immunogenicity:

Secondary immunogenicity objective #1 was to evaluate the Ab response to each vaccine dose level in adults aged 18 to 49 years, adults aged 65 to 79 years, and adults of Japanese descent aged ≥60 years.

Secondary immunogenicity objective #2 was to evaluate the Ab response to both 1 and 3 vaccine injections in adults aged 18 to 49 years at the middle dose level of mRNA-1345.

Secondary immunogenicity objective #3 was to evaluate the Ab response to a vaccine booster injection given approximately 12 months after the primary injection in adults aged 65 to 79 years.

The immunogenicity results are presented first for participants 18 to 49 years, followed from data for participants 65 to 79 years (*proposed target population*), including booster results and for the participants of Japanese descent ≥60 years.

1. Adults 18 to 49 Years

Neutralising Antibodies

Immunogenicity data for adults 18 to 49 years are presented after one Injection mRNA-1345 dose groups (50 µg, 100 µg and 200 µg) and after three injections mRNA-1345 (100 µg).

One Injection: Baseline nAb GMTs were comparable between the mRNA-1345 dose groups (750.1 to 1,252.6 IU/mL for RSV-A and 795.3 to 1,097.4 IU/mL for RSV-B) and the placebo group (1,581.0 IU/mL for RSV-A and 1,144.2 IU/mL for RSV-B), with overlapping 95% CI values across all groups.

A 3-dose series of 100 µg mRNA-1345 or placebo was administered to adults 18 to 49 years on Day 1, Month 2, and Month 4. One month after the first, second, and third mRNA-1345 vaccinations, respectively, the nAb GMFRs from prevaccination (Day 1) were 23.54, 21.19, and 15.56 for RSV-A and 16.02, 14.87, and 20.19 for RSV-B. These data support the administration of a single dose primary regimen of mRNA-1345 for subsequent studies.

Table 13 Study P101 RSV-A and RSV-B neutralising antibody titres after three 100 µg mRna-1345 injections (day 1, month 2, and month 4) by timepoint – adults 18 to 49 years of age – (per-protocol set)

Parameter / Time Point	100 µg mRNA-1345 Day 1, Month 2, and Month 4			Placebo Day 1, Month 2, and Month 4		
	N	GMT (95% CI)	GMFR (95% CI)	N	GMT (95% CI)	GMFR (95% CI)
RSV-A neutralizing antibodies (IU/mL)						
Baseline (Day 1)	19	811.9 (525.6, 1254.1)	-	4	2054.7 (1262.7, 3343.4)	-
Month 1	19	19,111.9 (12,383.9, 29,495.1)	23.54 (16.14, 34.33)	4	1988.9 (930.6, 4251.1)	0.97 (0.69, 1.35)
Month 3	13	17,802.2 (9821.8, 32267.0)	21.19 (11.53, 38.93)	3	1400.5 (555.1, 3533.8)	0.73 (0.35, 1.54)
Month 5	13	10,500.2 (61,44.7, 17,942.8)	15.56 (9.54, 25.38)	3	1909.1 (522.8, 6970.7)	1.00 (0.13, 7.46)
RSV-B neutralizing antibodies (IU/mL)						
Baseline (Day 1)	19	842.7 (494.3, 1436.5)	-	4	1373.7 (448.2, 4210.6)	-
Month 1	19	13,496.5 (8379.8, 21737.4)	16.02 (9.92, 25.87)	4	1640.5 (294.4, 9143.0)	1.19 (0.60, 2.38)
Month 3	13	13,400.3 (8814.8, 20,371.2)	14.87 (8.66, 25.54)	3	1324.8 (98.6, 17,800.2)	1.21 (0.37, 3.90)
Month 5	13	14,408.6 (8599.6, 24,141.7)	20.19 (12.20, 33.40)	3	1478.9 (79.2, 27,622.2)	1.35 (0.35, 5.23)

Binding Antibodies

One injection: Baseline PreF-bAb GMCs were comparable among the mRNA-1345 dose groups (5,812.9 to 7,722.4 AU/mL) and the placebo group (7,272.6 AU/mL), with overlapping 95% CI values across all groups. By 1 month postdose, the PreF-bAb GMCs in all the mRNA-1345 dose groups were higher compared with the placebo group.

Three Injections: Baseline PreF-bAb GMCs were comparable between the 100 µg mRNA-1345 (6,215.6 AU/mL) and placebo (9,290.5 AU/mL) 3-injection groups with overlapping 95% CI values. By 1 month postdose 1, the PreF-bAb GMCs in the mRNA-1345 dose group was higher (135,260.0 AU/mL) compared with the placebo group (10,307.3 AU/mL).

2. Adults 65 to 79 Years

Single Injection

Dose ranging: The nAb responses against RSV-A and RSV-B subtypes were evaluated after a single mRNA-1345 injection at all dose levels (12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg) in adults 65 to 79 years of age.

Dose selection: A dose of 50 µg mRNA-1345 was selected for advancement to the pivotal Phase 2/3 study (Study P301). At Month 1 postinjection, the RSV nAb response induced by 50 µg against both RSV-A (GMFR of 12.03 [95% CI: 8.78, 16.47]) and RSV-B (GMFR of 8.96 [95% CI: 6.79, 11.84]) support selection of this dose.

Table 14 Study P101 RSV-A and RSV-B neutralising antibodies through month 1 after a single injection by treatment group – adults 65 to 79 years of age (per-protocol set)

	Baseline		Month 1		
Parameter Dose Level	N	GMT (95% CI)	N	GMT (95% CI)	GMFR (95% CI)
RSV-A neutralizing antibodies (IU/mL)					
12.5 µg	46	1329.8 (969.1, 1824.8)	44	13,619.5 (9340.7, 19,858.3)	10.19 (7.17, 14.48)
25 µg	46	1519.0 (1128.8, 2044.0)	45	19,008.4 (14,470.5, 24,969.5)	12.17 (8.90, 16.64)
50 µg	47	1204.7 (918.5, 1580.0)	44	13,739.0 (9875.5, 19,113.8)	12.03 (8.78, 16.47)
100 µg	46	1224.9 (877.7, 1709.4)	43	17,053.4 (12,486.8, 23,289.9)	14.14 (10.23, 19.54)
200 µg	47	1879.9 (1403.5, 2517.9)	47	31,084.4 (24,302.8, 39,758.5)	16.54 (12.25, 22.33)
Placebo	58	1590.7 (1141.8, 2215.9)	56	1827.2 (1306.1, 2556.2)	1.15 (0.99, 1.34)
RSV-B neutralizing antibodies (IU/mL)					
12.5 µg	46	1437.5 (1015.1, 2035.4)	44	8154.1 (5568.1, 11,941.1)	5.29 (3.74, 7.49)
25 µg	46	1507.7 (1055.3, 2153.9)	45	10,235.2 (7445.9, 14,069.5)	6.56 (4.86, 8.87)
50 µg	47	1135.3 (833.2, 1547.0)	44	9432.1 (6706.2, 13,266.0)	8.96 (6.79, 11.84)
100 µg	46	941.0 (681.6, 1299.1)	43	9319.9 (6754.5, 12,859.7)	9.60 (7.31, 12.61)
200 µg	47	1455.4 (1008.2, 2100.9)	47	18,183.8 (13,206.2, 25,037.5)	12.49 (9.10, 17.16)
Placebo	58	1450.8 (1053.2, 1998.7)	56	1579.9 (1102.0, 2265.2)	1.12 (0.98, 1.29)

Abbreviations: CI = confidence interval; IU = international units; GMFR = geometric mean fold-rise, comparing postbaseline to baseline titre values; GMT = geometric mean titre; RSV = respiratory syncytial virus.

Source: Study P101 CSR Table 27, Table 28

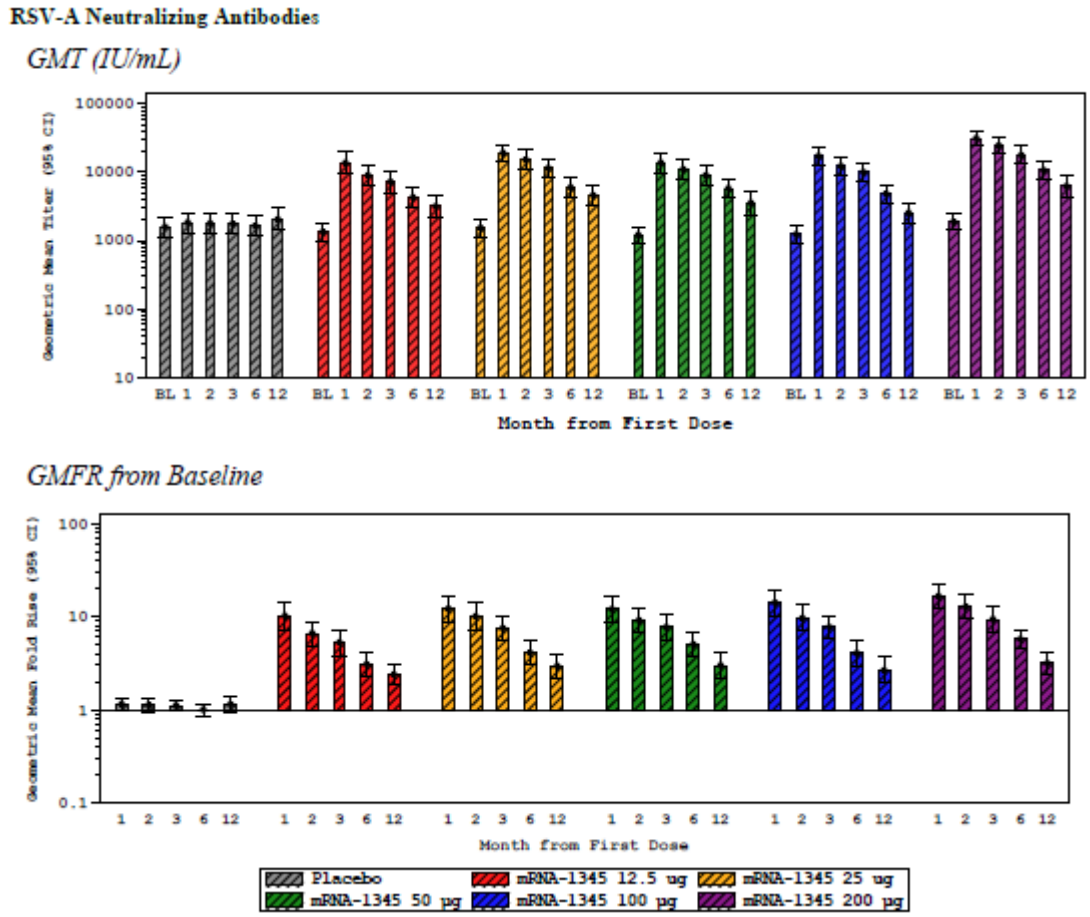
Neutralising Antibodies

Baseline nAb GMTs across mRNA-1345 dose groups ranged from 1,204.7 to 1,879.9 IU/mL for RSV-A and from 941.0 to 1,507.7 IU/mL for RSV-B, with overlapping 95% CI values across all groups.

By 1 month postinjection, the nAb GMTs in all the mRNA-1345 dose groups were higher for RSV-A (13,619.5 to 31,084.4 IU/mL) and RSV-B (8,154.1 to 18,183.8 IU/mL) compared with the placebo group.

The RSV-A and RSV-B nAb GMTs remained above baseline through 12 months postdose for all mRNA-1345 dose groups (GMFR ≥2.39 for RSV-A and ≥ 1.52 for RSV-B), demonstrating a persistence of immune response.

Figure 4: RSV-A neutralising antibodies - adults aged 65 to 79 years – (per protocol set)



Abbreviations: BL = baseline; CI = confidence interval; IU = international units; GMFR = geometric mean fold-rise;

GMT = geometric mean titre; LLOQ = lower limit of quantitation RSV = respiratory syncytial virus;

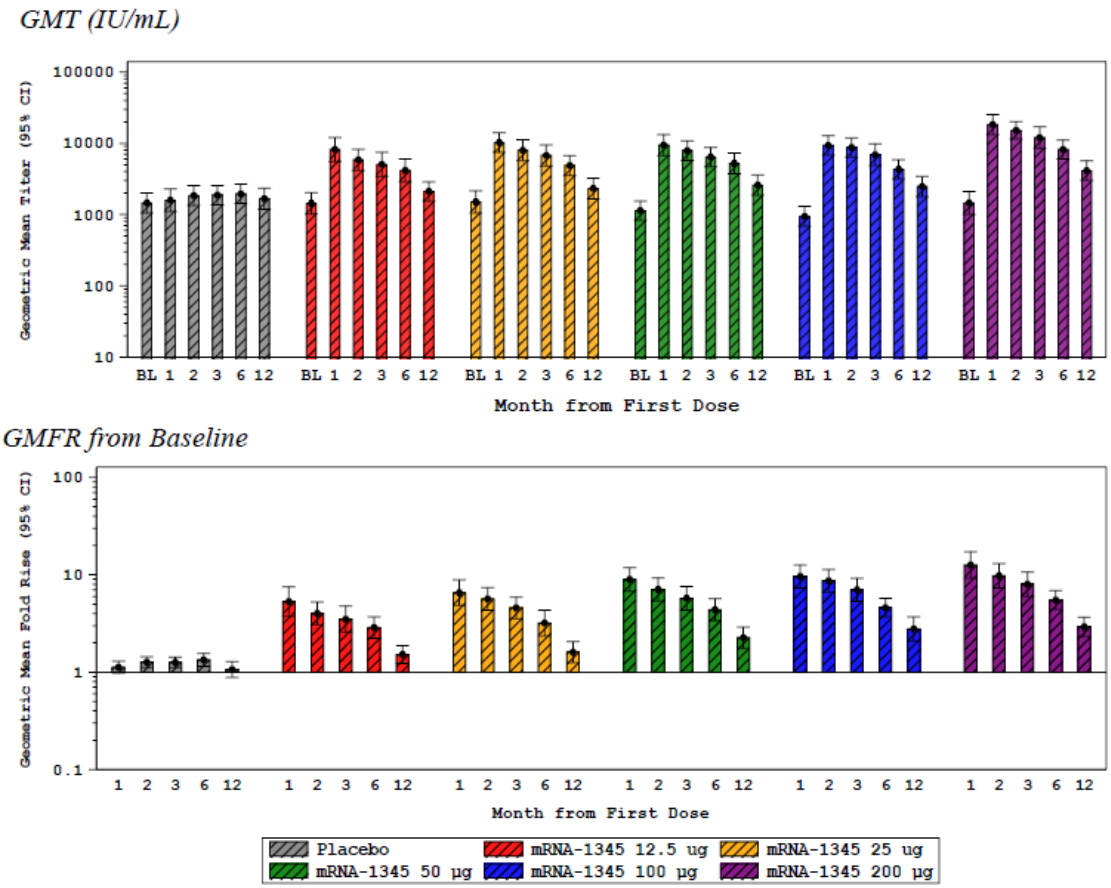
ULOQ = upper limit of quantitation.

Notes: For GMT calculations, antibody values reported as below LLOQ were replaced by 0.5 × LLOQ.

95% CIs were calculated using t-distribution of natural log-transformed values.

RSV-A (IU/mL): LLOQ=11, ULOQ=176,050.

Figure 5: RSV-B neutralising antibodies - adults aged 65 to 79 years – (per protocol set)



Abbreviations: BL = baseline; CI = confidence interval; GMFR = geometric mean fold-rise; GMT = geometric mean titre; LLOQ = lower limit of quantitation RSV = respiratory syncytial virus; ULOQ = upper limit of quantitation.

Notes: For GMT calculations, antibody values reported as below LLOQ were replaced by 0.5 × LLOQ.

95% CIs were calculated using t-distribution of natural log-transformed values.

RSV-B (IU/mL): LLOQ=8, ULOQ=111,998.

Source: Figure 14.2.1.2.1 and Figure 14.2.2.2.1

Binding Antibodies

Baseline PreF-bAb GMCs were comparable between the mRNA-1345 dose groups (6,960.5 to 9,173.2 AU/mL) and the placebo group (7,871.3 AU/mL), with overlapping 95% CI values across all groups. Baseline results were consistent with prior exposure to RSV.

Antibody persistence: One month after a single 50 µg mRNA-1345 vaccination, the nAb GMFR from baseline was 12.03 for RSV-A and 8.96 for RSV-B. RSV nAb titres remained above baseline through Month 12 (GMFR of 3.00 for RSV-A and 2.27 for RSV-B compared to baseline antibody titres), demonstrating the persistence of the immune response. A similar trend was demonstrated for RSV PreF bAb. In the 50 µg mRNA-1 345 dose group, the PreF bAb GMFR from baseline was 8.46 at Month 1 and 2.81 at Month 12.

Booster Injection

A booster 50 µg mRNA-1345 vaccination was administered approximately 12 months after the first 50 µg mRNA-1345 vaccination. The booster dose injection increased RSV-A and RSV-B nAb titres and PreF-bAb concentrations. At 1 month post the Month 12 mRNA-1345 booster injection, the 50 µg mRNA-1345/50 µg mRNA-1345 group showed nAb fold-rise from baseline (Day 1) was 7.29 for RSV-A and 5.20 for RSV-B, with 64.7% of participants with at least 4-fold increase for each RSV-A and RSV-B. At 1 month post the Month 12 mRNA-1345 booster injection, the PreF-bAb fold-rise from baseline (Day 1) was 7.03, with 70.6 % of participants demonstrating at least 4-fold increase.

Table 15: Study P101 RSV-A and RSV-B neutralising antibody titres after first and booster 50 µg mrna-1345 injection by timepoint – adults 65 to 79 years of age – (per-protocol booster subset)

Parameter Time Point	mRNA-1345 50 µg Day 1 and Month 12 Injections N	GMT (95% CI)	GMFR (95% CI)	Placebo Day 1 and Month 12 Injections N	GMT (95% CI)	GMFR (95% CI)
RSV-A neutralizing antibodies (IU/mL)						
Baseline (Day 1)	18	1038.7 (623.1, 1731.4)	-	51	1702.2 (1200.4, 2413.7)	-
Month 1 Post First Injection	17	9951.3 (5910.6, 16,754.4)	10.05 (5.47, 18.45)	49	1978.7 (1388.5, 2819.8)	1.16 (0.98, 1.38)
Month 12 Post First Injection	18	2791.9 (1756.5, 4437.8)	2.69 (1.81, 4.00)	49	2035.5 (1403.1, 2952.8)	1.15 (0.96, 1.38)
Month 1 Post Booster	17	8354.7 (5328.1, 13,100.4)	7.29 (4.25, 12.51)	48	2131.5 (1436.7, 3162.4)	1.24 (0.96, 1.58)
RSV-B neutralizing antibodies (IU/mL)						
Baseline (Day 1)	18	806.1 (513.0, 1266.4)	-	51	1507.5 (1086.3, 2092.2)	-
Month 1 Post First Injection	17	4770.2 (3117.9, 7297.9)	6.36 (3.85, 10.52)	49	1615.0 (1102.5, 2365.8)	1.11 (0.95, 1.30)
Month 12 Post First Injection	18	1984.9 (1331.4, 2959.1)	2.46 (1.78, 3.41)	49	1673.2 (1190.9, 2350.8)	1.07 (0.89, 1.29)
Month 1 Post Booster	17	4314.9 (3002.8, 6200.2)	5.20 (3.42, 7.92)	48	1740.1 (1180.7, 2564.6)	1.13 (0.92, 1.38)

Administration of an mRNA-1345 booster (50 µg) approximately 12 months after the first injection increased RSV nAb titres to levels similar to those after the initial injection (GMFR 1 month after the booster, relative to pre-first injection baseline, was 7.29 for RSV-A and 5.20 for RSV-B). These data indicate that, while the antibody titres remain above pre-vaccination levels 12 months after vaccination, a booster dose could be considered prior to the next RSV season.

An overview for nAb and PreF Binding Antibody Concentrations after a 50 µg mRNA-1345 Injection in Adults 65 to 79 Years of Age is presented in the table below.

Table 16: Study P101: RSV-A and RSV-B neutralising antibody titres and PreF binding antibody concentrations after a single 50 µg mRNA-1345 injection by timepoint – adults 65 to 79 years of age (per-protocol set)

Parameter Time Point	N	GMT or GMC (95% CI)	GMFR (95% CI)
RSV-A neutralising antibodies (IU/mL)			
Baseline (Day 1)	47	1204.7 (918.5, 1580.0)	—
Month 1	44	13,739.0 (9875.5, 19,113.8)	12.03 (8.78, 16.47)
Month 2	46	10,967.5 (7762.9, 15,494.9)	9.16 (6.73, 12.47)
Month 3	44	9020.8 (6523.6, 12,474.0)	7.53 (5.54, 10.24)
Month 6	43	5746.9 (4133.8, 7989.4)	5.05 (3.77, 6.76)
Month 12	39	3531.9 (2376.0, 5250.2)	3.00 (2.18, 4.13)
RSV-B neutralising antibodies (IU/mL)			
Baseline (Day 1)	47	1135.3 (833.2, 1547.0)	—
Month 1	44	9432.1 (6706.2, 13,266.0)	8.96 (6.79, 11.84)
Month 2	46	7905.3 (5765.3, 10,839.5)	7.08 (5.40, 9.28)
Month 3	44	6385.1 (4652.7, 8762.4)	5.62 (4.24, 7.45)
Month 6	43	5226.3 (3747.5, 7288.8)	4.38 (3.37, 5.70)
Month 12	39	2590.2 (1868.6, 3590.3)	2.27 (1.77, 2.91)
RSV PreF-binding antibodies (AU/mL)			
Baseline (Day 1)	47	7184.6 (5872.3, 8790.1)	—
Month 1	44	58,206.6 (46,911.4, 72,221.3)	8.46 (6.79, 10.55)
Month 2	46	50,630.1 (41,214.3, 62,197.1)	7.03 (5.75, 8.59)
Month 3	44	39,390.5 (31,889.7, 48,655.6)	5.44 (4.27, 6.92)
Month 6	43	27,977.0 (22,479.6, 34,818.8)	4.05 (3.34, 4.90)
Month 12	39	19,404.6 (15,117.4, 24,907.7)	2.81 (2.29, 3.44)

3. Adults of Japanese Descent Aged ≥60 Years

Neutralising Antibodies

Baseline nAb GMTs were comparable between the mRNA-1345 group (1,602.1 IU/mL for RSV-A and 1,029.4 IU/mL for RSV-B) and the placebo group (1,798.9 IU/mL for RSV-A and 1,275.6 IU/mL for RSV-B), with overlapping 95% CI. By 1 month postdose, the GMFR from baseline in the mRNA-1345 group was 11.15 for RSV-A and 6.60 for RSV-B, with at least 4-fold increase from baseline in 90.0% of participants for RSV-A and 75.0% of participants for RSV-B. The RSV-A and RSV-B nAb GMTs remained above baseline through 6 months postdose.

Binding Antibodies

Baseline PreF-bAb GMCs were similar among the 100 µg mRNA-1345 group (7,545.4 AU/mL) and the placebo group (6,680.8 AU/mL), with overlapping 95% CI. By 1 month postdose, the PreF-bAb GMC in

the mRNA-1345 group was higher compared to the placebo group and the PreF-bAb GMC in the mRNA-1345 group remained above baseline through 6 months postdose, demonstrating a persistence of immune response.

2. mRNA-CRID-001

Study mRNA-CRID-001 is an ongoing, open-label, randomised, Phase 1b study to evaluate the safety, reactogenicity, and immunogenicity of modified mRNA vaccines in healthy adults aged 18 to 75 years old to comprehensively assess innate and adaptive immune responses of mRNA lipid nanoparticle vaccines encoding different viral antigens. The vaccines to be tested in the study contain single mRNAs encoding cell-membrane associated antigens (SARS-CoV-2, RSV, CMV) and multiple mRNAs encoding influenza hemagglutinin A and B strains.

Study participants:

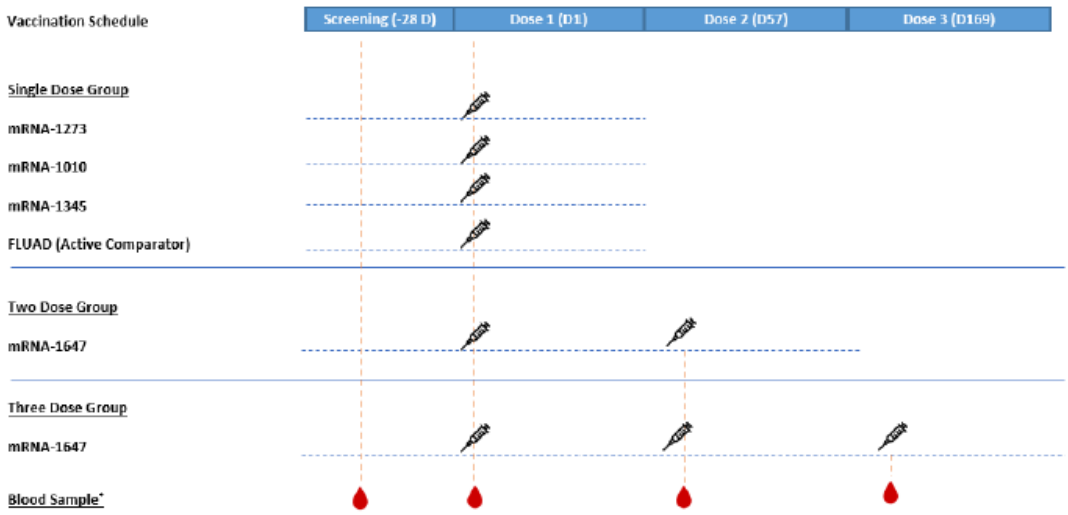
In part 1 were enrolled 120 participants, who were randomised to receive a single dose of mRNA-1345 (Day 1), 2 doses of mRNA-1647 (Day 1 and Day 57), or 3 doses of mRNA-1647 (Day 1, Day 57, and Day 169). For mRNA-1647, both CMV-seronegative and CMV-seropositive participants were enrolled in an approximately 2:1 ratio.

In part 2 were enrolled 180 participants, who were randomised to either mRNA-1010 or the active comparator (FLUAD®) and received the 2022-2023 Northern Hemisphere influenza strain-matched vaccines or mRNA-1273.

Study design

Approximately 8 sites in the US will participate in the study.

Figure 6: Study schema



Abbreviations: D = Day; mRNA = messenger ribonucleic acid; FLUAD = adjuvanted (MF59), inactivated, quadrivalent seasonal influenza vaccine.

Treatments

The vaccines to be tested in the study contain single mRNAs encoding cell-membrane associated antigens:

- mRNA-1273 (SARS-CoV-2); mRNA-1010 (influenza HA); mRNA-1345 (RSV); mRNA-1647 (CMV)
- Active comparator: adjuvanted MF59), inactivated, quadrivalent seasonal influenza vaccine (FLUAD)

Part 1 will enrol approximately 120 participants without a laboratory-confirmed infection or vaccination for RSV within 6 months of screening. Participants will be randomised to receive either a single dose of mRNA-1345, 2 doses of mRNA-1647 (D1 and D57), or 3 doses of mRNA-1647 on study D1, D57 and D169.

Part 2 will enrol approximately 180 participants without a laboratory-confirmed infection or vaccination for SARS-CoV-2 within 4 months, or influenza within 6 months of screening.

Sample size

There was no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety, reactogenicity, and immunogenicity of the study vaccines, including mRNA-1273, mRNA-1010, mRNA-1345, and mRNA-1647.

Overall, up to 300 participants will be randomly assigned to receive mRNA-1273, mRNA-1010, mRNA-1345, mRNA-1647, or FLUAD (active comparator) in the respective study part.

Randomisation

In Part 1 of the study, participants will be randomised with a 2:1:1 ratio into study arms 3,4, and 5, while Part 2 will have 2:2:2 randomisation for study arms 1, 2, and 6.

Blinding

There is no blinding in this study, as this is an open-label study.

Statistical Methods

The details of the statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalised before the clinical database lock for the study.

Results

Participants flow

In part 1 were enrolled 120 participants, who were randomised to receive a single dose of mRNA-1345 (Day 1), 2 doses of mRNA-1647 (Day 1 and Day 57), or 3 doses of mRNA-1647 (Day 1, Day 57, and Day 169). For mRNA-1647, both CMV-seronegative and CMV-seropositive participants were enrolled in an approximately 2:1 ratio.

In part 2 were enrolled 180 participants, who were randomised to either mRNA-1010 or the active comparator (FLUAD®) and received the 2022-2023 Northern Hemisphere influenza strain-matched vaccines or mRNA-1273.

The data snapshot for the preliminary analysis is 14 March 2023.

Recruitment

Up to 300 participants were enrolled. 120 participants were enrolled in part 1 and 180 participants were enrolled in part 2.

First Participant Enrolled: April 2022

The study is ongoing. Approximately 8 sites in the US will participate in the study.

Estimated Date Last Participant Completed: November 2023

Conduct of the study

There were two amendments of the protocol; the original version for this study is dated 03 Feb 2022; Amendment 1 (04 May 2022) and Amendment 2 (17 February 2023). An overview of the major protocol changes in Amendment 2 has been provided.

Baseline data

There were in total 61 participants aged 18-75 years old and the median age was 48.0 years. There were more females (68.9%) and mostly the participants were white (65.6%).

Outcomes and Estimations

Secondary immunogenicity

Secondary immunogenicity objective #2 was to evaluate the humoral immunogenicity of study vaccines at evaluable humoral immunogenicity timepoints.

The analyses of immunogenicity (secondary objective) will be based on the PP set and provided by vaccination group, unless otherwise specified. If the number of participants in the full analysis set (FAS) and PP set differ (defined as the difference divided by the total number of participants in the PP set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the immunogenicity endpoints, seroresponse rate from baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each postbaseline timepoint. Geometric mean of specific antibody titres with corresponding 95% CI at each timepoint and geometric mean fold rise (GMFR) of specific antibody titres with corresponding 95% CI at each post baseline timepoint over pre-injection baseline at D1 will be provided by treatment arm.

Exploratory immunogenicity objective #3 was to assess and characterise cellular, humoral, and mucosal immune responses, and peripheral blood cellular and plasma biomarkers to identify molecular mechanisms of mRNA vaccines.

Exploratory analyses may include, but not be limited to, biomarkers related to innate and adaptive immunity (T cell, B cell, inflammatory cytokines and chemokines) using high-dimensional flow cytometry, transcriptomic, epigenomic, and other methods.

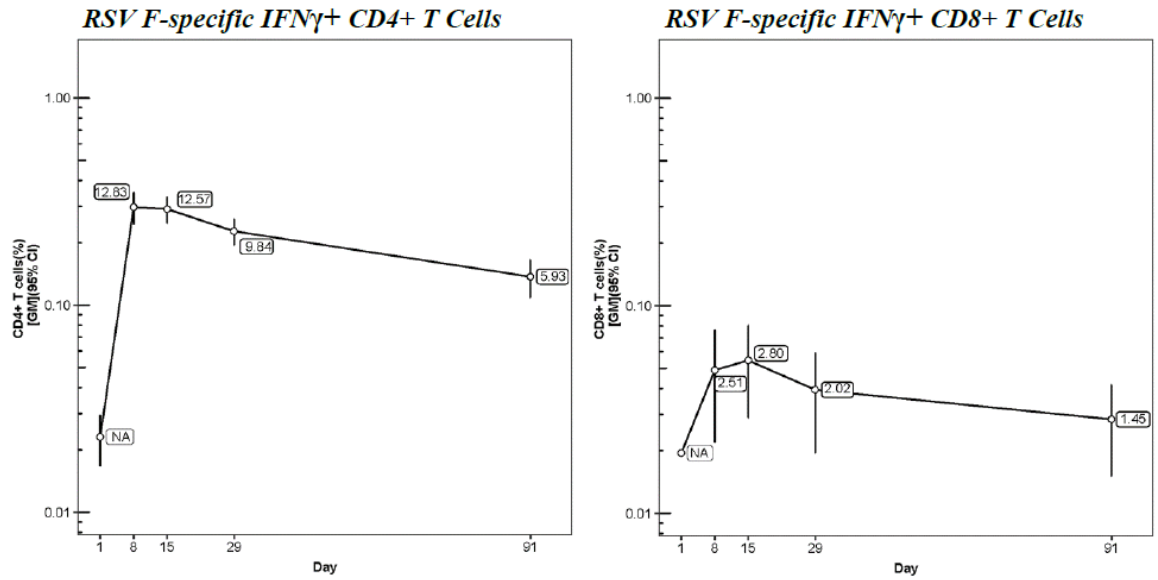
Results on cellular immunogenicity

Study CRID-001 evaluated cellular immune responses induced in adults following administration of a single dose (50 µg) of mRNA-1345. Peripheral blood mononuclear cells purified from blood samples collected on Days 1, 8, 15, 29 and 91 were tested for RSV F-specific CD4+ and CD8+ T cells using a flow cytometry-based intracellular cytokine staining assay. $CD4^+$ T cell cytokines elicited by vaccination were predominantly IFNγ, IL-2, and TNFα (Th1) and expressed the $CD4^+$ T cell co-stimulatory CD40L.

Results are displayed for IFNγ-secreting cells, which were represented at the highest frequency of observed responses. A single dose of mRNA-1345 induced measurable increases in both CD4+ and CD8+ IFNγ -producing T cells specific for RSV F in adults between 50 and 75 years of age. Responses peaked within 2 weeks of inoculation and remained elevated above baseline through Day 91. RSV F-specific $CD4^+$ T cells produced a pattern of cytokines consistent with a Th1 response as well as CD40 ligand expression, which itself is an important co-receptor for providing B-cell help.

Together with the results of Study P101, these results demonstrate that 50 µg mRNA-1345 induces both humoral and cellular immune responses in the target age group.

Figure 7: Study CRID-001: geometric mean frequency and 95% CI of RSV F-specific IFNγ+ CD4+ T cells and CD8+ T cells – adults 50 to 75 years of age



Abbreviations: CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; CI = confidence interval; CRID = clinical research for infectious diseases; F = fusion; GM = geometric mean; GMFR = geometric mean fold rise; IFNγ=interferon gamma; RSV = respiratory syncytial virus.

Values in the figures represent the GMFR from baseline. Error bars are 95% CI.

Source: Study CRID-001 Data Memo

2.6.6. Discussion on clinical efficacy

2.6.6.1. Design and conduct of clinical studies

- ***Pivotal efficacy clinical study mRNA-1345-P301***

The main study, mRNA-1345-P301, was designed as a seamless two-stage phase 2/3 study. It was a randomised, observer-blind, placebo-controlled study to evaluate the safety and efficacy of mRNA-1345 in Adults ≥60 Years of Age. Overall, the study design is considered acceptable. As the two-stage design—with enrolment of subjects during the RSV season 2021/2022 only in the U.S.A. and world-wide enrolment of subjects during the RSV season 2022/2023—was not considered in the analysis of results, the applicant was asked to carefully analyse the heterogeneity between study parts and to provide an analysis taking the two-stage adaptive design into account. As this was not adequately done in the first round of responses, a follow up question asking once more for analyses by study part was posed. With the D180 responses the applicant provided an assessment of VE with confidence intervals by study parts and results are provided in Accessory . The assessment was performed for both the Primary and Additional Analysis of efficacy. VE point estimates across study parts are comparable. The small number of total cases in the Phase 2 study aspect (n=8 for the 30Nov2022 data cut-off; n= 12 for the 30Apr2023 data cut-off) results in wide confidence intervals. From the perspective of the applicant the consistency across these assessments, together with the seamless transition between study phases, supports the overall analyses of VE for study P301. Based on the consistency in VE across P301 study parts, the applicant considers that no discussion of aspects raised in the former OC170 are required. The clinical OC31 was asking "If there are differences (between the

study parts), the aspects discussed in OC170 (LOQ) such as p-value combination, bias correction, assessment of different seasons and force of infection during these seasons, geographical differences might be helpful to provide further insights". As there are no obvious imbalances detected in the additional analysis of study parts no further discussion of the afore mentioned aspects is considered acceptable.

Accessory Table 17: Vaccine efficacy of mRNA-1345 against first episode of RSV-LRTD with 2 or more symptoms between 14 days and 12 months after injection, by study phases (PPE set)

Efficacy Analysis (Data cut-off date)	Study Phase	mRNA-1345 n/N (%)		Placebo n/N (%)		VE, % (95% CI)
Primary Analysis (30Nov2022)	Phase 2	1/966	(0.10)	7/977	(0.72)	85.3 (-19.6, 98.2)
	Phase 3	8/16606	(0.05)	48/16539	(0.29)	83.4 (64.9, 92.1)
Additional Analysis (30Apr2023)	Phase 2	3/969	(0.31)	9/981	(0.92)	66.0 (-25.8, 90.8)
	Phase 3	44/17143	(0.26)	118/17064	(0.69)	63.0 (47.8, 73.9)
N= number of participants in the PPE set n= number of participants with RSV-LRTD with 2 or more symptoms between 14 days and 12 months after injection. Vaccine efficacy (VE) is defined as 100% x (1 — hazard ratio (mRNA-1345 vs. placebo)). The VE and the CI for VE are based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect, adjusting for stratification factors at randomization.						

The study initially planned to randomise 34,000 subjects in a 1:1 ratio to mRNA-1345 or placebo. With Protocol Amendment 1 this was increased to 37,000 subjects, whereof 2,000 were to be randomised in Phase 2 and 35,000 in Phase 3. Overall, the sample size justifications were reasonable and comprehensible. However, it was stated that the sample size was driven by the "the number of cases required to demonstrate VE". This is not considered comprehensible as with a planned follow-up for the primary analysis of one year, the given attack rates would lead to much more events. Apparently, the follow up for the primary analysis was always intended to be much shorter than one year.

The study participants were randomly assigned to the study arms stratified by age and risk factors for LRTD. The latter were pre-specified in the protocol. However, investigators did not always follow these criteria. Concordance analyses were presented by the applicant showing that around 880 subjects among all 35,541 subjects (~2.5%) were wrongly allocated to strata. Sensitivity analyses of the primary endpoints were conducted using the actual risk factors for LRTD based on the data collected in the eCRF. No relevant differences were observed.

It is noted that the trial was a multiregional trial but randomisation was not stratified by regions. Without further justification this is not considered adequate and not understood (see ICH E17). Subjects were enrolled in 22 countries from 5 regions (North America: Canada, United States, Mexico; Middle and South America: Argentina, Chile, Colombia, Costa Rica, Panama; Europe: Belgium, Finland, Germany, Poland, Spain, United Kingdom; Africa: South Africa; Asia-Pacific: Australia, Bangladesh, Japan, New Zealand, Singapore, South Korea, Taiwan). Two subgroup analyses by regions were presented, one separating US and non-US participants and another one separating world bank regions (North America/Europe vs Central/Latin America/Africa vs Asia Pacific). Many of the regions are very heterogenous and hence regional effects cannot be fully excluded. This was also observed in the updated analyses presented with the Day 120 responses. Given the low effective sample size (number of RSV-LRTD events) additional subgroup analyses to rule out regional differences triggered e.g. by different enrolment times and/or different attack rates are not prompted for the time being. In future trials by the applicant it is expected that the randomisation will be stratified by geographical region, or an explanation will be provided in the protocol explaining the rational for the absence of stratification by geographical region.

A potentially major issue is the fact that the study was amended very late. Major changes to the trial design were implemented on 22 Sept 2022 and 16 Nov 2022, with a data cut-off date for the presented analyses just 14 days later (30 Nov 2022) and a DB lock on 25 Jan 2023. The SAP (v1) was finalised just one day before the data cut-off date 29 Nov 2022. An overview of key (statistical) changes can be found in **Error! Reference source not found.**.

The most relevant late changes to the study design affected multiplicity control and the success criterion:

- Up to Protocol Amendment 2 an O'Brien-Fleming alpha-spending approach was planned, were only 0.04% (one-sided) were to be used as significance level at the first interim analysis the majority of the significance level (2.27% one-sided) was to be saved for the primary analysis. With Amendment 2 this was changed to a Pocock alpha-spending approach, were 1.55% (one-sided) of the significance level were to be allocated to the first interim analysis and only 0.91% were saved for the primary analysis. This is theoretically a correct approach—yet very uncommon and was implemented very late. Upon request this change was justified by data shared for two other RSV vaccines at the US Advisory Committee on Immunization Practices (ACIP) meeting on 20 October 2022. This is not a strong rationale to use a specific spending function. However, sensitivity analyses using previously defined alpha-spending approaches at least provided reassurance that the primary endpoint (prevention of RSV-LRTD with ≥ 2 symptoms) would have been met under all protocol versions. The second primary endpoint (prevention of RSV-LRTD with ≥ 3 symptoms), however, was only met under the final protocol version.
- The success criterion was modified from requiring VE to be significantly greater than 30% to a threshold of 20%. This was also justified by data shared at the ACIP meeting. Indeed, both RSV vaccines were developed with a threshold of 20%.

The timing of the interim analysis was based on both primary endpoints. Analyses were planned to take place when both endpoints approximately have had the required number of events. The actual alpha spending was apparently based on the observed information fraction per endpoint. This is endorsed. The actual analysis took place when 64 cases (planned: 43 cases) met the case definition of RSV-LRTD with ≥2 symptoms and thereof 20 cases (planned: 16 cases) met the case definition of RSV-LRTD with ≥3 symptoms. According to the applicant, the higher number of events was driven by the faster accrual of events and the operational aspects with respect to data collection, data entry and event adjudication.

The currently defined primary estimand is not considered fully comprehensible (language not always in line with estimand framework) and some of the strategies to handle intercurrent events as well as the target population might be debatable. However, the estimate that tackles this estimand in essence is a standard per protocol analysis as usually submitted for vaccine efficacy studies. It currently seems that the issues around the definition of the estimand do not impact the overall conclusions in a meaningful way.

A futility analysis was planned in the original protocol in line with scientific advice but was removed in protocol amendment 1 because it was anticipated that the study enrolment would be nearly complete when the data and safety monitoring board (DSMB) reviewed the futility analysis results, due to a lower than projected RSV-LRTD case accrual rate. Therefore, no futility analysis on the efficacy of the product was performed and data from the Phase 2 segment and the study as a whole became a pivotal Phase 3 clinical trial. Immunogenicity data could have supported the Phase 2 component of the trial; however, no immunogenicity data from the pivotal phase 2/3 study as whole have been submitted in the initial submission.

- ***Supportive studies, mRNA-1345-P101 and mRNA-CRID-001***

Dose ranging phase 1 study mRNA-1345-P101

The mRNA-1345-P101 phase 1 dose-ranging clinical study involved primarily a single administration of mRNA-1345 at different doses levels and age groups. The study enrolled participants aged 18-49 years (n=100; Cohorts 1-4), RSV seropositive children aged 12-59 months (n=38-46; Cohorts 5 and 6 not included in the dossier); Older adults aged 65-79 years (n=300; Cohorts 7-11), Women of childbearing potential aged 18-40 years (Cohorts 12-14, not included in the dossier) and Japanese older adults aged >60 years (n=25).

Doses of 50 µg, 100 µg and 200 µg were tested in adults aged 18-49 years (Cohorts 1,2 and 4), and doses of 12.5 µg, 25 µg, 50 µg, 100 µg, 200 µg in older adults 65-79 years (cohorts 7-11). A subgroup of these older adult (65-79 years) in each dose group received a booster immunisation 12 months after primary vaccination. An additional group of Japanese older adults aged >60 years received a single administration of 100 µg (Cohort 15). One cohort of adults aged 18-49 years received three (100 µg) administrations at 2-month intervals (Cohort 3). Two other groups were also included but no data was provided, namely, seropositive children aged 12-59 months who received 15 µg and 30 µg mRNA-1345 (Cohorts 5 and 6), and a cohort of women of childbearing potential (WOCBP) aged 18-40 years who received single administrations of 12.5 µg, 25 µg and 50 µg respectively (cohorts 12-14). Data from the cohorts of younger adults aged 18-49 years was submitted as supportive data, although no reason was given for not including the WOCBP aged 18-40 years as supportive data, since inclusion of this groups would have provided supportive data for all the entire dose ranges assessed in the older adults.

Women of childbearing potential (WOCBP) aged 18-40 years constituted cohorts 12, 13 and 14 in the P101 study and received mRNA-1345 dosages of 12.5µg, 25µg and 50µg respectively. Upon request, a memo summarising interim immunological data in this cohort has been provided covering the time-period from Day 1 through EOS/6 months. Similar neutralising anti RSV-A and RSV-B GMT and GMFR were observed for the 25µg and 50µg doses respectively, although the titres were lower against RSV-B in agreement with results from other cohorts. Findings were numerically greater at 6 months post-vaccination also for the 25µg dose compared to the 50µg dose also regarding seroresponse rate for RSV-A responses. RSV-B responses were more consistent over time and similar between the 25µg dose and 50µg dose. Data for responses to PreF and postF conformations have been provided with higher baseline titres to postF conformation compared to preF conformation. Baseline neutralising antibodies were lower to both RSV-A and B compared to preF and post-F responses.

The primary endpoint of the phase 1 study was safety. The secondary objectives and endpoints assessed immunogenicity measuring GMT and GMFR as well as the proportion of individuals with >2 and>4-fold increases in antibody titre from baseline. Neutralising antibody responses to RSV-A and RSV-B, respectively, were assessed, as well as GMC for binding antibody responses to the PreF protein. PostF binding antibody responses were also measured but were not presented or discussed.

The applicant was asked to address both PreF and PostF responses according to dose, and the levels of PostF GMC compared to PreF GMC and their corresponding GMFR. Moreover, the applicant was also requested to discuss the results with respect to the potential for rare events of enhanced disease in individuals aged >60 years, who may require re-vaccination since their prior immunity is no longer evident.

In the applicant D120 responses, selected data were provided regarding responses to the PreF and postF domains in studies P101 and P301. Data from a later cut-off is requested for the P101 study including to all doses tested, and for the P301 study. Data on responses to the PreF and PostF domains

should be included in the immunogenicity results which are requested for the P301 study post D29. Furthermore, the data on preF and PostF responses should be included in the CSR for the P101 study for which data from a later cut-off have been requested. These requests are followed in the frame of RECs.

There were eight protocol amendments in total to this first in human dose-finding study. These included addition of different cohorts over time at different age groups and doses over time. Initially, the 50 µg dose in adults (18-49 years) was tested followed by the higher dose levels of 100 µg and 200 µg. No major differences were seen for the dose levels of 50 µg and 100 µg which prompted the inclusion of even lower dose levels; however, these were tested in older adults once the cohorts with the higher doses were already enrolled. This is not in accordance with general guidelines for first in human studies involving dose escalation. Since the higher doses appeared safe, it was acceptable to assess lower dose levels. Scientific advice had recommended that dose selection for further clinical development should be based on the cohorts aged 65-79 years where the chosen dose would elicit the highest GMT 1 month post immunisation with an acceptable safety profile. Should there be no important differences in the 1-month GMTs between some groups, the lowest dose among these groups should be selected. The further argumentations on the rationale of the dose selection provided in the D120 responses is acknowledged.

The primary vaccination part of the study has been completed, and booster immunisation part of the study is ongoing. Some immunogenicity data has been provided following booster immunisation, but on a limited number of participants at the selected dose (n=18) versus placebo (n=4). The applicant states that booster immunisation will be reported in a second CSR that has not been submitted. No claims regarding booster immunisation have been included in the SmPC.

- ***Study mRNA-CRID-001***

mRNA-CRID-001 was designed as an open-label, randomised, Phase 1b study to Evaluate the Safety, Reactogenicity and Immunogenicity of Modified mRNA Vaccines Using a Systems Biology Approach in Healthy Adults aged 18 to 75 years old. In Part 1 of the study, participants will be randomised with a 2:1:1 ratio into study arms 3,4, and 5, while Part 2 will have 2:2:2 randomisation for study arms 1, 2, and 6. There were two amendments of the protocol; the original version for this study is dated 03 Feb 2022; Amendment 1 (04 May 2022) and Amendment 2 (17 February 2023).

2.6.6.2. Efficacy data and additional analyses

- ***Study mRNA-1345-P301***

A total of 35 541 participants were randomised: 17 793 in the mRNA-1345 group and 17 748 in the placebo group. 99.7% and 99.6 % received injection in the two groups, respectively. In the randomisation set, at the time of data cut-off, 2.4 % of participants in the mRNA-1345 group and 2.5 % in the placebo group had discontinued from the study. The main reasons for withdrawal were lost to follow-up and withdrawal of consent.

Only a small proportion of participants were not included in the per-protocol efficacy set (PPE). Overall, 98.7 % of randomised participants were included in the PPE Set and among those included in the FAS, 0.9 % were excluded from the PPE Set. The most common reason for exclusion was not completing any visit or surveillance contact 14 days after vaccination.

Demographics and baseline characteristics are presented per safety population which was comparable to the FAS and were in general balanced between groups. The median age was 67.0 years and 51 % of participants were male. Participants > 80 years comprised only 5.6 %, while the targeted inclusion was

10 %. In addition, the number of participants with LRTD risk factors was relatively low with < 10 % of participants having LRTD risk factors. As these subgroups would likely benefit from an RSV vaccine, the applicant was asked to discuss if there are any plans to collect more data from subjects > 80 years of age and from subjects with underlying risk factors. The applicant clarified that CHF/COPD was used for stratification for study P301, but participants with other stable, chronic medical conditions were also included. Chronic heart and lung disease are known as two of the main risk factors for severe RSV disease, however, individuals with other medical conditions such as kidney disease, liver disease and diabetes mellitus, especially combined with age ≥ 60 years will also be at higher risk for severe RSV disease. The applicant stated that 29.3 % of participants reported at least one underlying condition putting them at higher risk for RSV-LRTD, including COPD, asthma, chronic respiratory disease, diabetes, CHF, advance liver disease or advance renal disease (comorbidities of interest).

The number of cases in the subgroup of participants with CHF/COPD were relatively small, resulting in wide CIs. For participants with comorbidities of interest the VE point estimate to prevent RSV-LRTD with ≥2 or more symptoms was 88.4% (95% CI: 49.9;97.3). The total number of participants with underlying risk factors for RSV-LRTD is considered sufficient.

The applicant has also initiated an immunogenicity and safety study in high-risk adults (mRNA-1345-P303) to collect additional data, intended to be submitted post-approval. In D180 responses the applicant committed to provide data from Study P303 (immunocompromised individuals and high-risk adults) post-authorisation in the framework of a REC, or a variation application as applicable. (**REC**)

The inclusion criteria stated that participants should have a BMI from < 18 kg/m2 to 35 kg/m2. However, in Table 11 in the CSR (Baseline characteristics, per-protocol efficacy set) it seems that the minimum BMI was 11.8 kg/m2 and the maximum BMI was 49.8 kg/m2, exceeding both minimum and maximum requirements according to the inclusion criteria. The applicant explained that despite investigator training that some participants verified to have met inclusion criteria had BMI out of range due to measurement or data entry error. These participants were only excluded from analysis subsets if there was a concern for subject safety or immunogenicity, and to make the study more generalisable, every effort was made to follow participants who were dosed as part of the study (in the interest of transparency and data integrity). The applicant was nevertheless asked how many participants this affected and to either redo the efficacy analysis excluding these participants or to justify why exclusion of these participants is unlikely to affect efficacy. In D180 responses the applicant provided an analysis of VE by the baseline BMI group (i.e. those with BMI ≤ 35 kg/m2 and those with BMI >35 kg/m2). No cases of RSV-LRTD were reported in participants with a BMI measure considered out of range, resulting in no meaningful change in the VE estimates for the primary efficacy endpoints provided in the submission. Therefore, it is considered unlikely that inclusion of participants with BMI out of range would have affected the overall outcome.

No data on immunocompromised individuals is included in the dossier. The applicant states that two large-scale active surveillance studies using administrative healthcare databases in the US and Europe will characterise the risk of predefined AESIs in the older population and within subgroups, defined by among others immunocompromised status. In addition, a study protocol (mRNA-1345-P303) was included in the dossier which describes that immunocompromised individuals aged ≥18 years, separated in a cohort of individuals aged 18-59 years and a cohort aged ≥60 years, will receive 2-doses of 50µg mRNA-1345 approximately 57 days apart. The study P303 is currently enrolling and the applicant committed to provide the data, post-authorisation in the framework of a REC, or a variation application as applicable.

In their Letter of Undertaking the applicant commits to provide data from Study P303 (immunocompromised individuals and high-risk adults) post-authorisation, by February 2027.

- ***Main efficacy results Study mRNA-1345-P301***

The applicant presented results from the initial IA1 with a cutoff date of 30 Nov 2022 and upon request presented results with a later cutoff date of 30 Apr 2023.

In the primary analysis (IA1), vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms, and VE of 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms was demonstrated. Therefore, the primary objectives according to the latest protocol version were met.

Sensitivity analyses were conducted based on actual strata, using the mITT Set and using the expanded case definition. In these sensitivity analyses no changes in case totals or case split was observed. An analysis that excluded cases of co-infection with other pathogens demonstrated a VE of 84.1% (95% CI: 66.4, 92,4) against RSV-LRTD with ≥2 symptoms, and VE of 81.3% (95% CI: 35.8, 94.6) against RSV-LRTD with ≥3 symptoms.

It was noted that the very early interim analysis led to a very short follow up time for individual participants in the primary analysis (data cutoff 30 November 2022). Additional Analysis results (data cutoff 30 April 2023) were presented upon request to substantiate the initial results. The median follow-up for the primary analysis of VE was 3.7 months, and for the additional analysis of VE was 8.6 months. In the additional analysis, >90% of participants were followed for at least 6 months following IP administration. While the data confirmed a clinically relevant VE it was considerably lower than the short-term VE observed in the primary analysis. Vaccine efficacy for the prevention of RSV-LRTD with ≥ 2 symptoms dropped from 83.7% (95% CI: 66.0%, 92.2%) to 63.3% (95% CI: 48.7%, 73.3%) and for the prevention of RSV-LRTD with ≥ 3 symptoms VE dropped from 82.4 (95% CI: 34.8%, 95.3%) to 63.0% (95% CI: 37.3%, 78.2%). This shows that the effect is not constant over time and the short-term effect observed in the primary analysis is not preserved. In addition, regional differences were observed at both data cutoffs. North America/Europe showed the lowest VE.

The SmPC was requested to be updated to reflect the results from the additional analysis Vaccine Efficacy. In D180 responses the applicant proposed to keep results from the primary analysis in the SmPC section 5.1 and to add information on the additional analysis. The applicant`s proposal contained a table (table 2) with VE results from both analyses. The applicant was further requested to delete results from the primary analysis from table 2 and maintain the results from the additional analysis both in table 2 and in the text. . The Committee advised that results from the primary analysis could be briefly described in the text but must not be presented in a dominant fashion. In response to this request the applicant agreed to the request to change section 5.1 of the SmPC as detailed above and provided a SmPC with these changes implemented. These changes are acceptable to the Committee.

The CHMP is of the view that the Primary and Additional Analyses of efficacy in the product information is crucial for maintaining transparency and scientific integrity. This approach ensures that healthcare providers receive a complete and accurate assessment of the vaccine's performance, which is essential for informed decision-making, and that individuals that may benefit from the vaccine have a chance to access it, without unnecessarily jeopardising the confidence of the medical community and the public in a safe and effective vaccine.

2.6.6.3. Overall Discussions on clinical efficacy

Sub-group analyses were conducted on strata such as age, sex, race, ethnicity, region, co-morbid conditions and other risk factors. These sub-groups had variable numbers of cases making analysis difficult. There was no tendency of lower VE in older sub-groups (although LB of CI in Age Group 1; ≥75 years was in the negative due to low numbers of participants and cases). VE in male and female is

comparable (84.1%, 83.4%). For participants with risk factors such as COPD/CHF the VE drops to 49.4% (CI: -457.9, 95.4) which is at least impacted by low numbers of participants (1217 and 1207, respectively) and low numbers of events (2 cases placebo group vs. 1 case mRNA-1345 group). Overall, VE point estimates for the sub-groups are in the range as for the PPE analysis.

The number of person years in the analyses of the primary objectives were comparable between the mRNA-1345 group and the placebo group. The numbers for patients at risk for the Cumulative Incidence Curves are decreasing dramatically after 3 months but numbers are comparable between the mRNA-1345 group and the placebo group indicating a comparable rate of enrolment and drop-out between these groups.

The applicant demonstrated a VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥2 symptoms of 91.7% (95% CI: 73.0%, 97.4%) against RSV-A and 68.5% (95%CI: 21.1%, 87.4%) against RSV-B. VE of mRNA-1345 to prevent the first episode of RSV-LRTD with ≥3 symptoms was 90.0% (95% CI: 22.0%, 98.7%) against RSV-A and 71.5% (95% CI: −37.0%, 94.1%) against RSV-B. The VE against RSV-B is lower compared to RSV-A although the F-protein is conserved between these RSV sub-types. Upon request the applicant clarified that the breakthrough cases were not different in RSV-A and RSV-B, which did not address the question of clinical implications of the lower efficacy against RSV-B. It is noted, though, that these subgroups are only defined based on the RSV-strain the subject was infected with. The strain which leads to an infection cannot be influenced and hence no action (such as exclusion of a subgroup from the label) can be taken here. It is noted that despite the lower effect in subjects with RSV-B, the overall effect is strong and clearly positive.

The key secondary objective relating to RSV-ARD was analysed with a total of 108 cases. The applicant provides a VE of 68.4% (95% CI: 50.9, 79.7) against RSV-ARD in the analysis with data cutoff 30 Nov 2022 and claimed an indication for protection against RSV-ARD after vaccination with mRNA-1345. With the updated analyses (cutoff 30 Apr 2023), the effect was further reduced to 53.9% (95% CI: 40.5, 64.3). The assessment of RSV-ARD was not planned until the 12 months analysis. No interim analysis was specified, which would justify the analysis of these data at an earlier time point and hence no type 1 error control exists for this and all subsequent endpoints in the hierarchy at this point in time. An updated analysis is expected to be submitted for all secondary endpoints under multiplicity control once the 12-month data is available. In D180 responses the applicant confirms that results from the Month 12 analysis of key and secondary endpoints (under multiplicity control) will be submitted for regulatory assessment in the framework of a variation application post-licensure when the data are available. The applicant commits that results from the Month 12 analysis of key and secondary endpoints will be submitted for regulatory assessment when the data are available (December 2024).

While indeed the endpoint overall shows a clinically relevant vaccine efficacy, this is primarily driven by preventing RSV-LRTD with 2 or 3 symptoms. The contribution of RSV cases with only 1 symptom is only marginal. This is evidenced by an analysis presented upon request where one can see that the VE against RSV with one symptom only is as little as 37.3% (95% CI: -15.1, 65.8). The case split was 17 cases with 1 symptom in mRNA-1345 arm, and 27 cases in placebo arm. For the updated analyses no analysis of VE against RSV with 1 symptom was presented. The case split (39 vs 58) indicates, however, that this effect would be even lower. There might be a protective effect even against RSV with 1 symptom but the effect can hardly be considered as clinically relevant. Taken together, results on the prevention of RSV-ARD is neither considered statistical nor clinically compelling and hence should be removed from the SmPC Section 5.1. In D180 responses the applicant stated that ARD has been removed from the SmPC section 5.1 and the revised Product Information has been provided within that response package.

The results from the study indicate less severe symptoms in the mRNA-1345 group compared to the placebo group. Cough and sputum production occurred at similar rates in the two groups, however, both fever and shortness of breath occurred at a higher frequency in the placebo group. In participants with RSV-LRTD with ≥ 3 symptoms, no fever occurred in the mRNA-1345 group, while 35.3 % of participants in the placebo group reported fever. Similarly, shortness of breath was reported in 33.3 % of the mRNA-1345 group, compared to 70.6 % in the placebo group.

Subgroup analysis of the primary endpoints are hampered by the small number of cases and group sizes, and although VE point estimates were similar to that of the overall PPE and case splits were favourable across subgroups, case numbers and groups size resulted in wide CIs and several subgroups were too small to generate meaningful point estimates, including in the protocol defined subgroups age and LRTD risk factors. The applicant states that the study was not powered to assess VE by subgroups and while this is accepted it would have been useful to have meaningful analyses, especially in the protocol defined subgroups (age and LRTD risk factors).

Immunogenicity data could have shed light on the immune response in the subgroups, as currently very little data are available regarding the response in subgroups**.** The inclusion of participants > 80 years of age were lower than the intended target. The applicant was asked to discuss if there are any plans to collect more data from subjects > 80 years of age.

The applicant informs that enrolment after first data cutoff date (30 November 2022) prioritised participants who had comorbidities and/or were ≥ 80 years old, raising the proportion of participants ≥ 80 years in the Additional Analysis of Efficacy to 7.9% and bringing the proportion closer to the intended target at 10 %. However, there are no cases in either placebo or active arm in this age group, hence there is no efficacy data. The efficacy in individuals ≥ 80 years old is uncertain due to the lack of cases.

The applicant has submitted a Global Immunogenicity Analysis Report which presents immunogenicity results at baseline and D29. The report indicates that the response at D29 in participants ≥ 80 years is similar to those <80 years. However, only 223 participants ≥ 80 years were included in the active arm. In addition, as there are no efficacy data and immunogenicity data are only through day 29, there is no information on the persistence of the immune response in this age group. Due to immune senescence, the duration of the response is likely shorter in individuals ≥ 80 years of age, however, as there is no efficacy data and no immunogenicity data beyond D29, the persistence of the immune response is not known.

Concerning other secondary and exploratory endpoints, no data have been submitted. The applicant has stated that other secondary and exploratory endpoints will be summarised in the future. It is expected that these data will be submitted as part of this procedure. Furthermore, in the initial IA no data on immunogenicity endpoints had been submitted, therefore it was not possible to assess immune responses in relation to the observed efficacy. In the D180 responses the applicant has provided immunogenicity data for study P301 up to day 29 only. However, data from later timepoints were requested based on the later cut-off for the CSR version 2.0, where sampling from day 181 could have been collected. These data are not forthcoming until the study is complete and the final CSR available.

The applicant commits to submit additional data for the remaining secondary and explorative objectives from study P301 post-authorisation as available, planned for a due date of July 2026. (REC) (cf letter of undertaking). Very little data is provided relating to persistence of protection. At the time of submission, for the PPE, 63 participants (34 in the mRNA-1345 group and 29 in the placebo group) had completed ≥12 months of follow-up and no cases of RSV-LRTD/ARD had been reported for this group beyond 12 months. The longest time frame of endpoints are 24 months.

As for the identification of a potential correlate of protection, the availability of immunogenicity data from the phase 2/3 study is eagerly anticipated. However, no details could be found on the size of the planned immunogenicity subset nor on any plans to establish a potential CoP.

Therefore, the applicant was asked to clarify the planned size of the immunogenicity subset and to clarify how its random selection will be performed. Furthermore, the applicant should detail any plans to identify a potential correlate of protection based on available data from their clinical trial programme. Finally, we would like the applicant to clarify planned subgroup analyses for the immunogenicity data and – if not already planned for – explore the effect of centre/region/country on the immunogenicity results. In the D120 responses the applicant provided the immunogenicity data for Study P301, including the analyses of immunogenicity by subgroups. The applicant is actively planning to perform a correlate analysis to assess immune markers as correlate of risk for RSV disease and/or correlate of protection against RSV disease. The analysis is ongoing, and the Applicant committed to provide a report once it is developed. Moreover, the applicant is committed to engage with the CHMP post-approval to discuss their plans to develop potential correlates of protection.

2.6.6.4. Overall Immunogenicity results for clinical study mRNA-1345-P301

In the D120 responses the applicant submitted the mRNA-1345-P301 Global Immunogenicity Analysis Report which presents immunogenicity results through Day 29:

Neutralising Antibodies

Baseline nAb GMTs (IU/mL) were similar in the placebo and mRNA-1345 groups for RSV-A and RSV-B.

In the mRNA-1345 group, administration of one dose of 50 µg of mRNA-1345 increased the GMT for RSV-A from 2552.82 IU/mL at Baseline to 21475.40 IU/mL at Day 29, representing a GMFR of 8.44.

The GMT for RSV-B increased from 1425.35 IU/mL at Baseline to 7245.98 IU/mL at Day 29, representing a GMFR of 5.11. For the placebo group, the Day 29 GMFR was 1.00 for RSV-A and 0.96 for RSV-B.

In the mRNA-1345 group, the Day 29 SRR for RSV-A was 74.2% and was 56.5%. Applying the pre-specified criterion of ≥2-fold increase, 91.4% of participants (RSV-A) and 84.3% of participants (RSV-B) achieved this increase.

Participants who met the SR criterion had a Baseline RSV-A nAb GMT of 2005.97 IU/mL; those not meeting the SR criterion had a GMT of 5062.52 IU/mL. A similar pattern was observed for RSV-B: participants who met the SR criterion had a Baseline nAb GMT of 1038.72 IU/mL whereas those not meeting a SR had a GMT of 2142.12 IU/mL. Data affirm that Baseline Ab levels influence fold-rise following vaccination and also highlight that participants not meeting the specified SR criterion have higher circulating levels of nAb available at the time of vaccination.

RSV-A and RSV-B nAb responses measured on Day 15 were consistent with Day 29 responses. In the mRNA-1345 group, the GMT for RSV-A nAb levels increased from 2552.82 IU/mL at Baseline to 28952.03 IU/mL at Day 15. GMT for RSV-B nAb levels increased from 1425.35 IU/mL at Baseline to 10311.00 IU/mL at Day 15. Similarly, SRR for RSV-A and RSV-B on Day 15 were generally consistent with the respective SRRs to Day 29. In the mRNA-1345 group, the SRR for RSV-A at Day 15 was 77.9% and for RSV-B was 67.6%.

The nAb GMT for the PPI Set at Baseline and at Day 29 are summarised by treatment group in the table below.

Table 18: Summary of RSV-A and RSV-B neutralising antibody levels (IU/mL) by visit (PPI set)

	RSV-A		RSV-B	
	Placebo (N=333)	mRNA-1345 50 µg (N=1515)	Placebo (N=333)	mRNA-1345 50 µg (N=1515)
Timepoint Data Category Statistic				
Baseline (Day 1)				
n[a]	333	1513	333	1512
GMT	2403.72	2552.82	1350.25	1425.35
95% CI[b]	(2136.01, 2704.98)	(2414.25, 2699.35)	(1203.25, 1515.20)	(1352.69, 1501.91)
Min, max	157, 106190	175, 259061	114, 79619	94, 112476
Day 29				
n[a]	332	1511	332	1509
GMT	2417.17	21475.40	1304.74	7245.98
95% CI[b]	(2155.94, 2710.04)	(20273.94, 22748.05)	(1159.97, 1467.58)	(6864.75, 7648.38)
Min, max	149, 89840	512, 259061	108, 77520	122, 112476
N1	332	1509	332	1506
GMFR	1.00	8.44	0.96	5.11
95% CI[b]	(0.95, 1.05)	(7.98, 8.92)	(0.90, 1.03)	(4.87, 5.37)
Seroresponse (%)[c]				
n (%)[d]	2 (0.6)	1119 (74.2)	5 (1.5)	851 (56.5)
95% CI[e]	(0.1, 2.2)	(71.9, 76.3)	(0.5, 3.5)	(54.0, 59.0)
≥2-fold increase from baseline[f]				
n (%)[d]	15 (4.5)	1379 (91.4)	18 (5.4)	1269 (84.3)
95% CI[e]	(2.6, 7.3)	(89.9, 92.8)	(3.2, 8.4)	(82.3, 86.1)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold-rise;

GMT = geometric mean titre; LLOQ = lower limit of quantification; max = maximum; min = minimum;

PPI = Per-Protocol Immunogenicity Set; RSV = respiratory syncytial virus; SRR = seroresponse rate;

ULOQ = upper limit of quantification.

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

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

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

c. Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold increase if Baseline was equal to or above the LLOQ. For RSV-A, LLOQ: 13 IU/mL, ULOQ: 259,061 UL/mL; for RSV-B, LLOQ: 10 IU/mL, ULOQ: 112,476 IU/mL.

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

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

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

Neutralising Antibody Responses by Subgroup

To assess nAb responses to mRNA-1345 in older individuals and those with underlying comorbidities, Day 29 RSV-A and RSV-B nAb GMT and GMFR were analysed by participant subgroups of the mRNA-1345 PPI Set.

Results of subgroup analyses demonstrated that mRNA-1345-induced nAb responses were largely consistent across age, gender, race, ethnicity, underlying disease, and geographic region. For both RSV-A and RSV-B, Day 29 nAb GMTs and GMFRs for the evaluated subgroups were generally consistent with those of the overall PPI Set.

Details are presented in the two tables below.

Table 19: Summary of RSV-A neutralising antibody (IU/L) responses for the mRNA-1345 treatment group by subgroup at day 29 (PPI set)

Subgroup	N (D1)	D1 GMT (95% CI)	D29 GMT (95%CI)	D29 GMFR (95% CI)
All	1513	2552.82 (2414.25, 2699.35)	21475.40 (20273.94, 22748.05)	8.44 (7.98, 8.92)
Age Group 1				
60 to 74 years	835	2437.76 (2267.89, 2620.35)	22491.95 (20887.08, 24220.14)	9.23 (8.57, 9.94)
≥75 years	678	2702.02 (2476.42, 2948.16)	20282.94 (18526.61, 22205.77)	7.56 (6.95, 8.22)
Age Group 2				
60 to 69 years	619	2308.99 (2123.48, 2510.72)	22611.81 (20733.81, 24659.90)	9.79 (9.00, 10.65)
70 to 79 years	671	2746.76 (2517.80, 2996.55)	20374.31 (18646.91, 22261.74)	7.46 (6.85, 8.12)
≥80 years	223	2706.13 (2344.61, 3123.39)	21811.74 (18680.71, 25467.55)	8.09 (6.98, 9.38)
Gender				
Male	833	2773.98 (2570.29, 2993.81)	20988.76 (19385.94, 22724.11)	7.58 (7.03, 8.19)
Female	680	2305.79 (2125.60, 2501.25)	22085.44 (20316.51, 24008.38)	9.62 (8.87, 10.43)
Race Group				
White	1170	2597.95 (2436.22, 2770.41)	21641.75 (20276.47, 23098.96)	8.37 (7.85, 8.92)
Black	133	2409.50 (1966.76, 2951.91)	21123.87 (17058.22, 26158.54)	8.76 (7.28, 10.53)
Asian	66	2548.85 (2001.56, 3245.80)	19071.18 (14629.42, 24861.54)	7.48 (5.98, 9.36)
Other	141	2344.99 (1992.61, 2759.69)	20881.19 (17381.78, 25085.13)	8.90 (7.44, 10.66)
Ethnicity				
Hispanic or Latino	705	2604.34 (2401.65, 2824.15)	22389.47 (20680.13, 24240.10)	8.60 (7.94, 9.31)
Non-Hispanic or Latino	787	2488.16 (2300.70, 2690.89)	20410.93 (18781.91, 22181.24)	8.25 (7.63, 8.93)
CHF/COPD				
Absent	928	2358.29 (2199.74, 2528.26)	19918.71 (18506.80, 21438.33)	8.47 (7.90, 9.08)
Present	585	2894.86 (2639.54, 3174.87)	24208.07 (22080.28, 26540.90)	8.39 (7.64, 9.21)
Comorbidities of Interest				
0	647	2410.09 (2216.15, 2621.00)	19270.14 (17641.68, 21048.92)	8.02 (7.39, 8.71)
≥1	866	2664.95 (2473.11, 2871.67)	23290.51 (21593.98, 25120.32)	8.76 (8.12, 9.46)
Frailty Status 1				
Fit (0-3)	1032	2520.87 (2358.55, 2694.37)	20826.41 (19428.39, 22325.03)	8.29 (7.77, 8.86)
Vulnerable (4-5)	310	2461.48 (2177.19, 2782.90)	21972.13 (19283.16, 25036.08)	8.93 (7.82, 10.19)
Frail (6 or More)	149	2900.00 (2367.79, 3551.83)	24951.46 (20768.11, 29977.47)	8.63 (7.16, 10.40)
Frailty Status 2				
Fit (0-3)	1032	2520.87 (2358.55, 2694.37)	20826.41 (19428.39, 22325.03)	8.29 (7.77, 8.86)
Vulnerable/Frail (4 or More)	459	2596.03 (2335.77, 2885.29)	22889.46 (20583.79, 25453.41)	8.83 (7.93, 9.83)
World Bank Region				
North America/Europe	684	2482.07 (2278.78, 2703.50)	20681.20 (18910.31, 22617.93)	8.38 (7.69, 9.13)
Central/Latin America/Africa	721	2625.21 (2424.77, 2842.21)	22957.46 (21199.79, 24860.86)	8.75 (8.09, 9.46)
Asia Pacific	108	2530.79 (2074.17, 3087.92)	17422.51 (14046.47, 21609.98)	6.96 (5.69, 8.53)
Region				
USA	573	2667.47 (2423.98, 2935.41)	21092.99 (19114.04, 23276.83)	7.95 (7.23, 8.75)
Non-USA	940	2485.37 (2321.08, 2661.28)	21711.73 (20229.51, 23302.55)	8.75 (8.17, 9.37)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GM = geometric mean; GMFR = geometric mean fold-rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; PPI = Per-Protocol Immunogenicity Set; RSV = respiratory syncytial virus; ULOQ = upper limit of quantification; USA = United States of America

Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ.

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

Table 20: Summary of RSV-B neutralising antibody (IU/mL) responses for the mRNA-1345 treatment group by subgroup at day 29 (PPI set)

Subgroup	N (D1)	D1 GMT (95% CI)	D29 GMT (95%CI)	D29 GMFR (95% CI)
All	1512	1425.35 (1352.69, 1501.91)	7245.98 (6864.75, 7648.38)	5.11 (4.87, 5.37)
Age Group 1				
60 to 74 years	834	1430.11 (1330.97, 1536.65)	7757.30 (7215.17, 8340.17)	5.45 (5.10, 5.82)
≥75 years	678	1419.51 (1315.11, 1532.19)	6662.01 (6144.25, 7223.40)	4.73 (4.40, 5.08)
Age Group 2				
60 to 69 years	617	1353.15 (1247.86, 1467.31)	7456.78 (6856.57, 8109.54)	5.54 (5.13, 5.98)
70 to 79 years	672	1498.21 (1382.00, 1624.19)	7092.51 (6531.94, 7701.17)	4.76 (4.43, 5.13)
≥80 years	223	1416.24 (1244.39, 1611.83)	7139.03 (6211.84, 8204.61)	5.05 (4.47, 5.71)
Gender				
Male	831	1487.12 (1383.80, 1598.16)	7170.16 (6651.75, 7728.97)	4.83 (4.52, 5.16)
Female	681	1353.43 (1254.37, 1460.32)	7339.99 (6791.17, 7933.17)	5.48 (5.10, 5.89)
Race Group				
White	1169	1458.39 (1374.63, 1547.25)	7329.21 (6896.00, 7789.65)	5.06 (4.79, 5.34)
Black	133	1263.69 (1028.70, 1552.36)	6702.84 (5498.63, 8170.77)	5.29 (4.38, 6.41)
Asian	66	1188.62 (924.91, 1527.53)	5775.01 (4495.28, 7419.05)	4.91 (3.98, 6.06)
Other	141	1453.14 (1244.77, 1696.39)	7631.36 (6379.75, 9128.52)	5.25 (4.46, 6.19)
Ethnicity				
Hispanic or Latino	704	1688.33 (1570.32, 1815.20)	8554.02 (7925.51, 9232.37)	5.08 (4.74, 5.45)
Non-Hispanic or Latino	787	1218.53 (1131.78, 1311.94)	6164.04 (5715.55, 6647.72)	5.10 (4.77, 5.46)
CHF/COPD				
Absent	928	1325.59 (1242.96, 1413.71)	6801.42 (6345.60, 7289.98)	5.15 (4.83, 5.48)
Present	584	1599.54 (1464.38, 1747.16)	8012.58 (7353.64, 8730.56)	5.06 (4.68, 5.47)
Comorbidities of Interest				
0	647	1317.80 (1220.19, 1423.21)	6474.15 (5962.96, 7029.16)	4.92 (4.57, 5.29)
≥1	865	1511.49 (1407.96, 1622.63)	7881.57 (7339.04, 8464.21)	5.26 (4.93, 5.62)
Frailty Status 1				
Fit (0-3)	1032	1414.57 (1326.76, 1508.19)	6937.15 (6491.79, 7413.07)	4.94 (4.66, 5.23)
Vulnerable (4-5)	309	1404.04 (1255.88, 1569.67)	7680.39 (6831.26, 8635.06)	5.51 (4.91, 6.18)
Frail (6 or More)	149	1568.42 (1319.74, 1863.95)	8730.36 (7368.85, 10343.43)	5.55 (4.73, 6.51)
Frailty Status 2				
Fit (0-3)	1032	1414.57 (1326.76, 1508.19)	6937.15 (6491.79, 7413.07)	4.94 (4.66, 5.23)
Vulnerable/Frail (4 or More)	458	1455.53 (1325.43, 1598.41)	8005.09 (7271.01, 8813.27)	5.52 (5.03, 6.06)
Wold Bank Region				
North America/ Europe	683	1253.56 (1155.67, 1359.73)	6377.87 (5871.16, 6928.31)	5.12 (4.76, 5.52)
Central/Latin America/ Africa	721	1656.67 (1543.04, 1778.67)	8476.41 (7865.28, 9135.01)	5.12 (4.77, 5.49)
Asia Pacific	108	1176.55 (965.13, 1434.30)	5682.39 (4655.62, 6935.60)	4.99 (4.18, 5.96)
Region				
USA	572	1313.55 (1200.35, 1437.43)	6411.45 (5852.25, 7024.07)	4.92 (4.54, 5.34)
Non-USA	940	1497.98 (1405.45, 1596.61)	7807.96 (7305.20, 8345.31)	5.23 (4.92, 5.56)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GM = geometric mean;

GMFR = geometric mean fold-rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; PPI = Per-Protocol Immunogenicity Set;

RSV = respiratory syncytial virus; ULOQ = upper limit of quantification; USA = United States of America

Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ.

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

Binding Antibodies

Baseline RSV preF bAb GMCs were comparable between the placebo and mRNA-1345 groups: 10194.25 AU/mL in the placebo group and 10729.51 AU/mL in the mRNA-1345 group. At Day 29, RSV preF bAb GMC was higher in the mRNA-1345 group (81884.16 AU/mL) compared to the placebo group (10060.15 AU/mL), representing a GMFR of 7.65. Day 29 GMC in the placebo group remained similar to Baseline. RSV preF bAb SRR at Day 29 was 79.1% in the mRNA-1345 group. Additionally, 94.2% of mRNA-1345 participants achieved a ≥2-fold increase in GMC.

A summary of Baseline and Day 29 RSV preF bAb GMC in the PPI Set is presented in the Table below.

Table 21: Summary of RSV binding antibody levels (preF; AU/mL) by Visit (PPI set)

Baseline (Day 1)		
n[a]	333	1513
GMC	10194.25	10729.51
95% CI[b]	(9374.48, 11085.69)	(10310.57, 11165.47)
Min, max	1104, 91124	798, 464148
Day 29		
n[a]	333	1511
GMC	10060.15	81884.16
95% CI[b]	(9258.94, 10930.70)	(78644.23, 85257.58)
Min, max	1153, 81862	1063, 580553
N1	333	1510
GMFR	0.99	7.65
95% CI[b]	(0.96, 1.01)	(7.33, 7.98)
Seroresponse (%)[c]		
n (%)[d]	1 (0.3)	1195 (79.1)
95% CI[e]	(0.0, 1.7)	(77.0, 81.2)
≥2-fold increase from Baseline[f]		
n (%)[d]	3 (0.9)	1423 (94.2)
95% CI[e]	(0.2, 2.6)	(92.9, 95.4)

Abbreviations: CI = confidence interval; GM = geometric mean; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; LLOQ = lower limit of quantification; max = maximum; min = minimum; PPI = Per-Protocol Immunogenicity Set; RSV = respiratory syncytial virus; ULOQ = upper limit of quantification.

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

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

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

c. Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold increase if Baseline was equal to or above the LLOQ. preF LLOQ: 35 AU/mL, ULOQ: 580,553 AU/mL.

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

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

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

Binding Antibody Responses by Subgroup

Baseline and Day 29 RSV preF bAb GMCs for the mRNA-1345 subgroups are presented in the Table below. The same subgroups were examined for bAb as for nAb.

Table 22: Summary of RSV binding antibody (PreF, AU/mL) responses for the mRNA-1345 treatment group by subgroup at day 29 (PPI set)

Subgroup	N (D1)	D1 GMC (95% CI)	D29 GMC (95%CI)	D29 GMFR (95% CI)
All	1513	10729.51 (10310.57, 11165.47)	81884.16 (78644.23, 85257.58)	7.65 (7.33, 7.98)
Age Group 1				
60 to 74 years	834	10274.12 (9753.88, 10822.10)	86856.32 (82437.96, 91511.49)	8.46 (8.00, 8.95)
≥75 years	679	11316.57 (10640.77, 12035.29)	76148.48 (71511.87, 81085.72)	6.75 (6.33, 7.20)
Age Group 2				
60 to 69 years	618	9986.69 (9408.92, 10599.95)	86548.13 (81459.26, 91954.90)	8.68 (8.13, 9.27)
70 to 79 years	672	11081.34 (10436.73, 11765.76)	77891.62 (73262.68, 82813.03)	7.05 (6.61, 7.52)
≥80 years	223	11876.87 (10597.00, 13311.31)	81611.90 (72874.50, 91396.89)	6.87 (6.14, 7.69)
Gender				
Male	832	11622.25 (11010.29, 12268.23)	80839.73 (76587.43, 85328.13)	6.97 (6.59, 7.37)
Female	681	9731.34 (9181.54, 10314.07)	83182.35 (78271.41, 88401.41)	8.56 (8.02, 9.14)
Race Group				
White	1170	10871.17 (10389.14, 11375.57)	81076.23 (77466.45, 84854.22)	7.48 (7.12, 7.85)
Black	133	10038.97 (8616.39, 11696.43)	80354.04 (70105.03, 92101.40)	7.99 (6.88, 9.27)
Asian	66	10111.41 (8372.77, 12211.08)	75200.51 (60627.30, 93276.73)	7.44 (6.26, 8.83)
Other	141	10598.21 (9442.00, 11895.99)	92505.93 (80813.51, 105890.06)	8.73 (7.59, 10.04)
Ethnicity				
Hispanic or Latino	704	11112.18 (10482.61, 11779.56)	90222.15 (85323.51, 95402.04)	8.13 (7.64, 8.66)
Non-Hispanic or Latino	788	10358.26 (9810.90, 10936.15)	74698.02 (70516.37, 79127.65)	7.23 (6.82, 7.66)
CHF/COPD				
Absent	929	9883.89 (9427.36, 10362.52)	75746.68 (71989.86, 79699.55)	7.68 (7.28, 8.10)
Present	584	12226.25 (11405.37, 13106.22)	92695.66 (86844.79, 98940.71)	7.60 (7.08, 8.16)
Comorbidities of Interest				
0	647	9942.90 (9396.44, 10521.15)	73099.86 (68809.56, 77657.66)	7.37 (6.93, 7.84)
≥1	866	11357.54 (10748.75, 12000.82)	89146.73 (84497.15, 94052.16)	7.86 (7.41, 8.33)
Frailty Status 1				
Fit (0-3)	1033	10381.67 (9897.14, 10889.92)	78989.01 (75263.86, 82898.53)	7.63 (7.26, 8.02)
Vulnerable (4-5)	309	10962.66 (10094.50, 11905.47)	83549.64 (75964.75, 91891.87)	7.62 (6.87, 8.45)
Frail (6 or More)	149	12422.22 (10674.80, 14455.67)	96247.42 (84846.12, 109180.80)	7.72 (6.68, 8.93)
Frailty Status 2				
Fit (0-3)	1033	10381.67 (9897.14, 10889.92)	78989.01 (75263.86, 82898.53)	7.63 (7.26, 8.02)
Vulnerable/Frail (4 or More)	458	11417.62 (10600.74, 12297.45)	87466.85 (81050.64, 94390.98)	7.65 (7.04, 8.32)
World Bank Region				
North America/Europe	685	10400.37 (9785.41, 11053.97)	74788.39 (70305.46, 79557.17)	7.20 (6.75, 7.68)
Central/Latin America/ Africa	720	11004.68 (10394.99, 11650.13)	91025.72 (86061.73, 96276.04)	8.29 (7.79, 8.81)
Asia Pacific	108	11042.96 (9641.89, 12647.63)	71574.25 (61551.99, 83228.40)	6.52 (5.62, 7.56)
Region				
USA	574	10662.23 (9958.33, 11415.88)	73614.39 (68752.28, 78820.35)	6.92 (6.44, 7.43)
Non-USA	939	10770.84 (10257.48, 11309.90)	87370.68 (83149.64, 91805.99)	8.13 (7.71, 8.57)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GM = geometric mean; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; LLOQ = lower limit of quantification; PPI = Per-Protocol Immunogenicity Set; RSV = respiratory syncytial virus; ULOQ = upper limit of quantification; USA = United States of America

Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ.

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

In the applicant's D120 responses immunogenicity data on study P301 are submitted, including the nAb and bAb responses measured from placebo and mRNA-1345 recipients at Baseline and Day 29. In addition, results on the Ab responses obtained on Day 15, have been included while the applicant explained that additional timepoints will be analysed at a future date.

Baseline nAb GMTs (IU/mL) were similar in the placebo and mRNA-1345 groups for RSV-A and RSV-B. In the mRNA-1345 group at Day 29 the nAb GMT levels were increased for both RSV-A and RSV-B compared with the Baseline levels respectively, for RSV A_D29 GMT (95%CI):21475.40 (20273.94, 22748.05) and with a D29 GMFR (95% CI) 8.44 (7.98, 8.92); for RSV B_ D29 GMT (95%CI) 7245.98 (6864.75, 7648.38) and with a D29 GMFR (95% CI) 5.11 (4.87, 5.37). A higher nAb response against RSV-A (8.44-fold) compared to RSV-B (5.11-fold) is observed.

In the subgroup analyses considering the Age group 1, it is observed a slightly lower humoral immune response with increasing of age. Therefore, higher neutralising antibody titres (nAb GMT) for RSV-A and for RSV-B were observed in the age group 60-74 years old compared with the age group ≥75 years. Accordingly, for RSV-A at Day 29 GMT (95%CI) was 22491.95 (20887.08, 24220.14) and GMFR was 9.23 (8.57, 9.94) for the age group 60 to 74 years vs. D29 GMT (95%CI) 20282.94 (18526.61, 22205.77) and GMFR 7.56 (6.95, 8.22) for the age group ≥75 years. The same trend it is seen for the RSV-B, respectively at Day 29 (Age Group 1) GMT was 7757.30 (7215.17, 8340.17) with GMFR 5.45 for the age group 60 to 74 years vs. GMT 6662.01 (6144.25, 7223.40) and GMFR 4.73 for the age group ≥75 years. In the Age group 2 it is observed higher nAB response in the age group 60 to 69 years, a slightly drop for the 70 to 79 years and slightly increase for the age group ≥80 years for both RSV A and RSV B.

Regarding the binding AB the baseline RSV preF bAb GMCs were comparable between the placebo and mRNA-1345 groups: 10194.25 AU/mL (95% CI: 9374.48, 11085.69) in the placebo group and 10729.51 AU/mL (95% CI: 10310.57, 11165.47) in the mRNA-1345 group. At Day 29, RSV preF bAb GMC was higher in the mRNA-1345 group (81884.16 AU/mL [95% CI: 78644.23, 85257.58]) compared to the placebo group (10060.15 AU/mL [95% CI: 9258.94, 10930.70]), representing a GMFR of 7.65 (95% CI: 7.33, 7.98). Day 29 GMC in the placebo group remained similar to Baseline.

RSV preF bAb SRR at Day 29 was 79.1% (95% CI: 77.0%, 81.2%) in the mRNA-1345 group. Additionally, 94.2% (95% CI: 92.9%, 95.4%) of mRNA-1345 participants achieved a ≥2-fold increase in GMC. The applicant has submitted also the Baseline and Day 29 RSV preF bAb GMCs for the mRNA-1345 subgroups. The same subgroups were examined for bAb as for nAb. Slightly higher bAB response is observed in the Age Group 1 for the age 60 to 74 years with GMC (95%CI) 86856.32 (82437.96, 91511.49) and GMFR 8.46 compared to the age group ≥75 years with GMC (95%CI) 76148.48 (71511.87, 81085.72) and GMFR 6.75. In the Age group 2 it is observed the same trend as for the nAB. It is acknowledged that while some individual Day 29 GMT or GMFR differed from those of the overall PPI Set, no pattern emerged to suggest clinically meaningful differences in population subgroups for nAb responses. In summary, results show that mRNA-1345 enhanced levels of nAb against both RSV subtypes and of bAb, and these were observed across population subgroups.

The applicant stated that correlate of protection analyses for nAbs in Study P301 are underway. Reasonable comparison between the immunogenicity results from study P301 and the immunogenicity results provided from the supportive study P101 cannot be concluded at this point of time.

The P301 study included immunogenicity analyses at a number of different time points beyond D29 (Months 6, 12, 18 and 24), which will provide an indication of antibody persistence and could be viewed in relation to the observed vaccine efficacy at later timepoints. GMT of serum neutralising antibodies were to be determined as well as GMFR and the proportion of participants with a >4-fold increase in antibody titre from baseline and up to 24 months later (Key secondary endpoints).

Additional vaccine efficacy data has been provided based on the later cut-off date. Corresponding immunogenicity data has not been provided beyond D29 which was an expectation based on communication at the pre-submission meeting.

The current procedure is an application for a full marketing authorisation.

All available data on immunogenicity for RSV-A and RSV-B at all time points should be provided according to the secondary and explorative objectives and endpoints from Study P301. This is especially important concerning the oldest age groups (> 80 years) as no events have been reported in either placebo or active arm and thus no efficacy can be estimated in this subgroup. In D180 responses the applicant has provided immunogenicity data for study P301 up to day 29 only. However, data from later timepoints were requested based on the later cut-off for the CSR version 2.0, where

sampling from day 181 could have been collected. These data are not forthcoming until the study is complete and the final CSR available. The applicant commits to submit additional data for the remaining secondary and explorative objectives from study P301 post-authorisation as available (cf letter of Undertaking).

2.6.6.5. Dose ranging phase 1 study mRNA-1345-P101

The phase I first in human, dose finding mRNA-1345 P101 study was carried out exclusively in the United States (21 sites). Immunogenicity formed secondary endpoints.

A single administration was used for primary vaccination. Justification for the single dose was based on the assumption that the target population in the study, and the sought indication, are non-naïve. RSV infection is widespread, and it is anticipated that adults and elderly will have been exposed previously. However, the duration of immunity following natural infection will also wane over time, rendering some individuals susceptible to reinfection. It is therefore not clear that a single dose (to boost responses to prior infection) is sufficient or whether a regimen of more than one dose may be required to reinstate immunity in some individuals (re-vaccination). The first-in-human P101 study did not address a second dose in the elderly aged 65-79.

One subgroup aged 18-49 was given three doses (100µg per dose) at months 0, 2 and 4. The objective was to provide data that could support future primary vaccination in children which is beyond the scope of this application for a marketing authorisation. However, it is nevertheless unclear why only the 100µg dose was investigated and not another dose level in addition such as the 50µg dose. This could have provided evidence supporting the proposed posology of a single dose in adults >60 years. Furthermore, it is anticipated that responses in children are likely to be greater than in adults and the elderly. Immune responses (neutralising antibody responses to RSV-A and RSV-B respectively) were found to increase substantially after the first immunisation and were maintained up to 6 months after the third dose compared to a single dose.

In the Day 120 responses the applicant explained that a subgroup of adults between the ages of 18-49 years (n=20) received 3 injections of 100 µg mRNA-1345 at 2-month intervals (i.e. Baseline and Study Month 2 and Month 4). To assess the maintenance of GMT over time, blood samples are available from each group at 6 months after the last injection: (i) for the 3-injection group, this is Study Month 10, 6 months after the 3rd injection at Study Month 4; (ii) for the 1-injection group, this is Study Month 6. For these timepoints, serum antibody results were available from 12 adults in the 3-injection group and 19 adults in the 1-injection group. Based on the data provided (tables 24 and 25 in the P101 CSR), there did not appear to be any substantial benefit of a 3-injection primary series compared to a single dose primary immunisation.

The main aim of the phase 1 study was to select the mRNA-1345 dose for further clinical development. The P101 study recruited healthy individuals, adults in care homes were excluded. The sought indication is for adults aged >60 years, however, immunogenicity data is only available for the age group 65-79 years as specified in the study protocol. Throughout the study, neutralising antibody responses to RSV-A were consistently higher than neutralising antibody responses to RSV-B. This is understandable since mRNA-1345 is based on the RSV-A A2 strain. This strain should be specified in the SmPC**.** The applicant has explained that changes have been made to the sequence so that referring to the strain RSV-A A2 will no longer be accurate. Although it is acknowledged that modifications have been made to the sequence, it is evident that the product is based on RSV-A rather than RSV-B by virtue of immune data obtained so far and vaccine efficacy.

Reference to the mRNA being derived from RSV-A should be included in the SmPC section 2. Cross-reactivity to RSV-B should be included in section 5.1 of the SmPC. In D180 responses the applicant stated that the SmPC section 2 has been revised.

The size of each cohort was limited with 46 participants receiving the 25µg dose and 47 receiving the 50µg dose. The placebo group included 58 participants.

Neutralising antibody responses to RSV-A increased after the first immunisation for all doses tested with GMFR of 12.17 (25µg); 12.03 (50µg) fold over baseline (GMT: 19008.4 and 13739.0 respectively). The GMT also increased for higher doses (100µg and 200µg), but it is anticipated that these dose levels will be associated with greater safety concerns. At month 12 post-vaccination, GMFR were reduced to 2.96 (25µg); and 3.00 (50µg) fold above baseline. For RSV-B, the fold increases from baseline were lower than for RSV-A. One month post vaccination for the group receiving 25 µg the RSV-B GMFR was 6.56 and 8.96 for the 50-µg dose (corresponding GMT were 10235 and 9432) respectively. Although the GMT and GMFR were similar for both the 25 µg and 50 µg doses, the 50µg dose was selected for further clinical development. This was based on balancing the induced immune responses and reactogenicity profile. However, it is anticipated that the 25-µg dose would have a better safety profile than the 50 µg and the dose selection requires further justification.

In the D120 responses, the applicant provided a thorough explanation on the dose selection prioritising the clinical aspects, i.e. based on the immunogenicity and reactogenicity profile of the selected 50 µg dose. The 50-µg dose showed a comparable reactogenicity profile compared to the 25-µg dose and no clinical significant differences were noticed. The selected dose (50 µg) optimised the immune responses in the elderly population and also noted to elicit RSV-specific cellular responses in Study CRID-001. However, it should be noted that cellular responses to the 25µg dose is not known since it was not determined in the CRID-001 study. It is acknowledged that no efficacy data is available for the 25µg dose, although both doses show similar immunogenicity and reactogenicity in the P101 study. The applicant argues that the 50µg dose in the population >60 years and according to the indication is considered suitable since this age group includes individuals with immune senescence. This could suggest that a different dose may be considered for the younger adult age groups. RSV is a common infection so it is anticipated that adults will have some pre-existing immunity to RSV. Efficacy data is only available for the 50µg dose, it therefore remains to be seen what the level of reactogenicity will emerge once the product is authorised and used more widely.

Based on these further argumentations the rationale on the dose selection is acknowledged. A single mRNA-1345 vaccination boosted both RSV-A and RSV-B nAb titres as well as RSV PreF-bAb concentrations at all dose levels evaluated in adults aged 18 to 49 years, adults aged 65 to 79 years, and adults of Japanese descent aged 60 years and older.

At matched mRNA-1345 dose levels, the RSV GMT and nAb fold-rise from baseline was numerically higher in adults aged 18 to 49 years than adults aged 65 to 79 years. The clinical relevance of this observation cannot be concluded in the absence of immunogenicity results which are derived from the study in which efficacy has been determined, e.g. immunogenicity results from study P301.

In adults aged 18 to 49 years, a second and third mRNA-1345 vaccination at 2 and 4 months did not further boost RSV antibody levels compared to a single vaccination.

The immunogenicity data in adults aged 18 to 49 years old demonstrated that there is no clear dose response relationship and it is not clearly understood how these data do changes over time. It is acknowledged that the antibody kinetics over time could not be derived from small studies such as Study P101. However, it is reassuring that the review of antibody levels did not show decay over time and in addition the applicant confirmed that longer term antibody kinetics following booster administration are ongoing.

In adults aged 65 to 79 years (targeted population) at one month after a single injection of 50 µg mRNA-1345, a rise was shown in the neutralising antibody titres (nAb GMT) for RSV-A and for RSV-B, followed by a decline through Month 6 with persistence above baseline levels through Month 12 (GMFR of 3.00 for RSV-A and 2.27 for RSV-B). Slightly lower nAbs titres were observed against RSV B than against RSV A.

The RSF PreF binding antibodies showed a rise from baseline to 8.46 at Month 1, then a decline through Month 6 (4.05), maintaining a persistence through Month 12 (2.81).

Waning of immunity in terms of nAbs and binding Abs is demonstrated overtime until Month 12 with neutralising antibodies (GMTs) still higher than baseline. However, the immune response observed cannot be directly translated to efficacy as there is no correlate of protection, while the immunogenicity data from the efficacy study P301 have been submitted in the D120 responses (Global Immunogenicity Analysis Report).

Natural exposure to RSV during study conduct could have an impact on the results provided. As seen for booster vaccination the GMTs do not rise further but stay at a higher level compared to single vaccination which might lead to over-estimation of the persistence of the humoral immune response. Upon request the applicant explained that the analysis of the Study P101 placebo group across timepoints serves to identify community RSV transmission in a contemporaneous control group. Results through to study month 14 (including blood obtained at Baseline, Month 1, 2, 3, 6, 12,13 and 14), showed no meaningful increases in Ab levels across studied timepoints. Results from the placebo control group help address concerns that enhanced Ab levels observed in mRNA-1345 recipients reflect responses to vaccination rather than natural infection.

The humoral immunogenicity data from this ongoing supportive Phase 1 study are based on a limited targeted population for the sought indication (adults 65 to 79 Years) of 59 participants, respectively 47 participants in the 50 µg mRNA-1345 (Per Protocol Set group) and 12 participants in the placebo group. Therefore, the immunogenicity data from the pivotal study are considered important.

In the applicant's D120 responses have been provided the immunogenicity data from the pivotal study, however reasonable comparison between the immunogenicity results from study P301 and those provided from the supportive study P101 cannot be concluded at this point of time. Follow up questions on immunogenicity data for both studies are raised.

Lower humoral immune response can be seen with increasing of age (higher neutralising antibody titres (nAb GMT) for RSV-A and for RSV-B in the age group 18-49 years old compare with the age group 65 to 79 years old. This is not unexpected; however, the clinical relevance of the differences cannot be determined in the absence of efficacy results which are tied to immunogenicity results.

Each dose-level cohort in the age group 65-79 years received a second administration of the same dose or placebo at month 12. One month post-booster immunisation, the GMT had increased and the GMFR were 7.25 and 7.29 for the 25 µg (n=22) and 50 µg (n=17) dose levels respectively.

Upon request of the CHMP the applicant elaborated more on the booster responses compared with the primary vaccination and the 'baseline titres' in the placebo group.

Review of nAb responses in older adults in Study P101 showed that for all dose levels evaluated, the 95% CI for GMFRs against RSV-A and RSV-B 1 month after the 12-month booster overlapped with GMFRs at 1 month after the first vaccination. Further conclusions are precluded based on the small group sizes, which limit assessment of influence of baseline titres on post-vaccination responses in Study P101.The applicant clarified that in the placebo group of older adult cohorts, RSV-A and RSV-B neutralising antibody GMTs did not change substantially from Baseline to Month 14. In placebo recipients, the GMFR at Month 12 is 1.15 (95% CI 0.96, 1.38). This is based on the neutralising

antibody GMT responses in participants with non-missing data at Month 12 (n=49) compared to those same participants at Baseline.

Data is only available to month 14 where the GMFR remained essentially stable. The booster part of the study is ongoing and the applicant states that the data will be presented in a separate CSR. Further follow-up data is nevertheless requested even though it is acknowledged that a booster immunisation is not claimed in the SmPC. However, data from the placebo group will provide persistence data following primary vaccination up to 24 months post-primary vaccination once the study is complete**.** No further data on persistence of immune responses from the P101 study is included in this submission. The clinical study report for the P101 study is based on cut-off for adults aged 65-79 (03 October 2022, Month 14) (interim analysis). Data from a later cut-off should be provided so that it is possible to gauge the persistence of immune responses over time post-vaccination based on available data. The placebo arm from the booster vaccination would allow for persistence data beyond one year. Available data from immunogenicity endpoints and time-points as specified in the protocol from a later cut-off should be provided for the P101 study. In D180 responses the applicant stated that all available immunogenicity data for study P101 have already been provided. The study is anticipated to be completed shortly, in July 2024. The applicant is requested to provide the final CSR including data from all immunogenicity endpoints and time-points as specified in the protocol as soon as possible post-authorisation.

The applicant commits to provide the final P101 CSR including data from all immunogenicity endpoints and time-points as specified in the protocol as soon as possible post-authorisation (cf letter of undertaking).

The applicant was asked to discuss the plans to assess the need for further doses in the longer term. In the D120 responses the applicant explained that the timing of the future booster doses will be evaluated in two studies included in the RMP as category 3 studies (Study P302 Part C- 1-year booster dose/post primary dose and Study P301 Part B 24-month booster dose/6-month extension). The Data from Studies P302 Part C and P301 Part B, included in the RMP as a category 3 studies, should be provided post-authorisation.

The applicant commits to provide data from Study P302 Part C (12 months revaccination) and P301 Part B (24 months revaccination), included in the RMP as a category 3 studies, post-authorisation (REC)

In addition to neutralising antibodies to RSV-A and RSV-B, binding antibodies to the PreF and postF proteins were measured. However, no data relating to postF antibody responses have been included or discussed in the CSR. The fusion protein (F) has been modified so that it is stabilised in the preF conformation. This stabilisation is described in the SmPC section 5.1 to be through 'structural engineering'. This is a very general statement which the applicant simply deleted. It is suggested that in place of the term 'structural engineering' it should be possible to state 'stabilised in the prefusion domain though changes in amino acid sequence of RSV-A'. Furthermore, section 5.1 can describe cross-reactivity between RSV-A and RSV-B. In D180 responses the applicant stated that the SmPC section 5.1 has been revised accordingly.

The binding antibody data is presented as GMC rather than titre (GMT). This change to the protocol was introduced in Amendment 7. Upon request the applicant acknowledged a typographical error in the Protocol Amendment 7 for reporting of binding antibody data (GMT rather than GMC), which has been corrected. Binding data for the study was always intended to be reported in AU/mL as geometric mean concentration (GMC).

In the D120 responses, the applicant provided further information on the immunogenicity assays used in the pivotal phase 3 clinical study (mRNA-1345-P301) and the corresponding validation reports.

The concentrations of binding antibodies to the PreF domain were similar for the 25 µg and 50 µg dose levels in the age group 65-79 years. One month post vaccination, the GMFR was 8.40 and 8.46 for the 25 µg and 50 µg dose levels respectively. The GMC declined over time and at month 12 were 2 to 3-fold above baseline values as was observed for the neutralising antibodies to RSV-A and RSV-B respectively. Baseline GMC for PostF binding antibodies was slightly higher for the PostF GMC, however, the GMFR for PostF binding antibodies one month post-vaccination were 5.86 and 5.91 for the 25 µg and 50 µg dose levels respectively, lower than for the PreF GMFR which had corresponding GMFR of 8.40 and 8.46 for the 25 µg and 50 µg dose levels respectively. However, the GMFR was reduced at 12 months post-vaccination to 2-3 times baseline values. The applicant has not discussed the PostF binding antibody responses. Although mRNA-1345 is based on the PreF confirmation, there is cross-reactivity to the PostF conformation which is also enhanced following vaccination. This suggests that vaccination can stimulate potential pre-existing PostF antibody responses or responses that are cross-reactive with PreF. The applicant was requested to discuss the results with respect to the potential for rare events of enhanced disease in individuals aged >60 years, who may require re-vaccination since their prior immunity is no longer evident**.** Upon request, the applicant provided binding antibody (bAb) results measured against preF and postF Studies P101 and P301.

However, data on responses to the PreF and PostF domains should be included in the immunological data requested for the P301 study post D29. Furthermore, the data on preF and PostF responses should be included in the CSR for the P101 study where data from a later cut-off have been requested. In D180 responses the applicant explained that the P301 immunogenicity report, provided as part of this procedure, includes binding antibody responses to both the PreF and PostF conformations of the RSV fusion protein through D29. Furthermore, the applicant commits to submit data on responses to the PreF and PostF domains for the P101 study from a later cut-off as data are available post-authorisation. Therefore, the applicant is requested to provide the final CSR for the P101 study as soon as possible post-authorisation since this study is due to be completed in July 2024. In addition, the applicant is requested to provide the final CSR for study P301 when available. (**REC**) (cf. letter of undertaking)

In adults of Japanese descent aged ≥60 Years, a single injection of 100 µg mRNA-1345 elicited robust and persistent nAb responses against RSV-A and RSV-B subtypes, with higher RSV nAb titres then baseline levels through 6 months postinjection. At 1-Month postvaccination, the GMFRs which were almost similar in magnitude to those in adults 65 to 79 years of age who received the same mRNA-1345 dose level.

Participants of Japanese descent were followed for 6 months in contrast to the age group 65-79 years. Similar observations were made regarding lower neutralising antibody responses to RSV-B compared to RSV-A and was in agreement with the other age-group cohorts where data has been submitted. This data is supportive since it uses a higher dose than that proposed for this application for marketing authorisation and involves a lower sample size.

Data in Japanese adults $\underline{\geq}$60 years is included in the dossier as supportive information. These participants received a single dose of 100µg which is not in accordance with the proposed indication. This population was included in the mRNA-1345-P101 study to enable evaluation of mRNA-1345 in subsequent late-stage clinical studies in Japan. The applicant was requested to clarify why only the 100µg dose was selected for evaluation in the Japanese population for primary vaccination. The sought posology is a single dose of 50 µg. The applicant states that the study in the Japanese population was initiated before the dose for the Phase 2/3 P301 study was defined. Although this explanation is acknowledged, it is unclear why two doses were not assessed in this population. This would have provided more supportive data to dose selection for the phase 2/3 study P301.

The humoral immunogenicity analysis from Study P101 do have a database lock date of Feb 2023. The cellular immediate immunity analysis from Study CRID-001 is dated of 14 March 2023. The applicant provided the P101 WOCBP Data Memo, which summarises antibody responses in WOCBP and no later data memos are available. Available data from immunogenicity endpoints and time-points as specified in the protocol from a later cut-off for the Study P101 study should be provided pre-authorisation. The estimated end of study time-point should be provided. In D180 responses the applicant stated that available data from immunogenicity endpoints in Study P101 (including assessments 12 months post-primary vaccination) and in the pivotal Study P301 (Day 29 post-vaccination) have been submitted within the MAA. No additional timepoints for immunogenicity assessments from Study P101 are available for submission within this procedure (Study P101 last participant, last visit is anticipated in July 2024). The applicant committed to submit data for subsequent immunogenicity timepoints post-authorisation as available. Therefore, the final CSR for study P101 including data from all immunogenicity endpoints and time-points as specified in the protocol should be provided as soon as possible post-authorisation.

The applicant commits to provide the final P101 CSR including data from all immunogenicity endpoints and time-points as specified in the protocol as soon as possible post-authorisation (cf letter of undertaking).

Comparisons of immunogenicity across studies were not possible at the initial submission as Efficacy analyses (VE) were performed only for Study P301, and immunogenicity data are only available for Study P101. In the applicant D120 responses, immunogenicity data were submitted for Study P301 up to D29, however reasonable comparison between the immunogenicity results from study P301 and those provided from the supportive study P101 cannot be concluded at this point of time. Follow up questions on immunogenicity data for both studies are raised.

Overall it can be concluded from the submitted immunogenicity results study P101 that the mRNA-1345 vaccine is able to induce a durable immune response in the intended target population. A trend of lower immune response with increasing age is observed. However, the immunogenicity subset is based on a limited number of participants for the target population. Immunogenicity data from the pivotal study P301 has only been provided up to D29.

- **Study mRNA-CRID-001**

Study mRNA-CRID-001 evaluates the Safety, Reactogenicity and Immunogenicity of Modified mRNA Vaccines Using a Systems Biology Approach in Healthy Adults aged 18 to 75 years old.

The CMI form an exploratory endpoint, and data is available for 30 participants aged 18-75 years that received mRNA-1345. The participants were stratified with n=15 aged 18-49 and n=15 aged 50-75 years. The data snapshot for the preliminary analysis is 14 March 2023.

Among the 15 participants between 50-75 years old in the randomised subset, the median age was 57.0 years. There were more females (60.0%) compared to males (40.0%) participants. Mostly the participants were White (60.0%) compared to other races; (33.3%) were Black and (6.7%) were Asian. CD4+ T cell responses were observed in nearly all participants assessed in the 50- to 75-year-old age group and in all participants in the 18- to 49-year-old age group. The responses were maintained above baseline through Day 91 and consistent with an expansion of the memory CD4+ T cell response to RSV pre-F. In addition, mRNA-1345 elicited CD8+ T cell responses following vaccination in both age groups, but these were lower in frequency than the CD4+ T cell responses.

RSV-F-specific CD4+ and CD8+ responses were evaluated in the days after vaccination up to day 91. The CD4+ cytokines were predominantly IFNγ, IL-2 and TNFα as part of Th1 cytokines. The CD8+ responses were of low frequency. This study has not been formally submitted as part of the dossier.

Reference is made to cell-mediated immune responses in the SmPC. Since this data does not form part of the clinical trials for evaluation, and only a CSR 'Memo' has been submitted where these data correspond to an exploratory endpoint and not part of the pivotal phase 3 study, reference to CMI should be removed from the SmPC. Upon request the applicant has revised the text on the mechanism of action in section 5.1 of the SmPC and streamlined the description of the cellular immune responses following intramuscular administration of the vaccine. Although there is very little data to support the induction of cell-mediated immunity specifically, the statement relating to cellular immunity and can be considered acceptable.

In addition, the assay used for the CMI has been established but not qualified or validated. In the applicant's Day 120 response, was provided a description on the development pathway of the intercellular cytokine stain flow cytometry assay used for CMI analysis. Data was reported after subtracting the background, thus confirming that the reported T cell responses were specific to RSV Pre-F antigen (mRNA-1345). However, caution may need to be exercised when interpreting these data, because the assay used in this study was not validated.

The peak magnitude of T-cell responses was slightly lower in adults 50 to 75 years of age than it was in adults 18 to 49 years of age, as expected. The same trend was observed with the humoral immune response with increasing of age.

There were no results submitted regarding the humoral immunogenicity of the study vaccine in study mRNA-CRID. The applicant committed to share the data of cellular and humoral responses in the final study CSR post-approval.

The applicant committed in D180 responses to submit the final CSR for Study mRNA-CRID (including humoral and cellular data) post-approval (cf letter of undertaking). Upon request the applicant explained that data from co-administration studies, including the co-administration of mRNA-1345 and high dose flu vaccine (Study mRNA-1345-P304) will be available post-approval. The applicant committed in D180 responses that data from co-administration studies (Study P302 Parts A and B and Study P304) will be provided post-authorisation (cf letter of undertaking).

The immunogenicity/efficacy data in the immunocompromised individuals might be different from those observed in the overall population. The applicant is conducting Study mRNA-1345-P303 to describe responses in immunocompromised individuals aged 18 and older. This study is currently enrolling, and results will be shared once available, post-approval for regulatory review. The applicant committed in D180 responses that data from Study P303, including the final CSR will be provided post-authorisation (cf letter of undertaking).

The data from Study mRNA-CRID-001 might become supportive and of relevance once the applicant will provide the CMI results from the pivotal study in order to make comparison of CMI results across studies.

Additional expert consultation

Not applicable

2.6.7. Conclusions on the clinical efficacy

The final indication wordings proposed by the applicant are acceptable to the CHMP.

The immunogenicity data up to D29 from the pivotal study have been submitted in the applicant D120 responses. The presentation of VE in the SmPC section 5.1 and the description of the stabilisation in

Pre-F conformation have also been addressed. Additional results that have been requested but are not available to date and therefore the CHMP considers the following measures necessary to address issues related to efficacy:

Table 23: Conclusion on the clinical efficacy

Area	Description	Due Date
Clinical	The applicant commits to send the EIRs (Establishment Inspection Reports) when available for the two clinical trial sites where GCP inspections have been carried out (Study P301), when available (REC).	When available
Clinical	The applicant commits that all GCP non-compliance issues for the entire study P301 will be included in the final CSR. The final CSR should be submitted on completion of the study (REC)	July 2026
Clinical	The applicant commits that results from the Month 12 analysis of key and secondary endpoints (Study P301) will be submitted for regulatory assessment when the data are available (REC)	Data memo December 2024
Clinical	The applicant commits to submit additional data for the remaining secondary and explorative objectives from study P301 post-authorisation as available (REC)	July 2026
Clinical	The applicant commits to provide data regarding 24-month booster immunisation in Study P301 (REC)	Data memo September 2025
Clinical	The applicant commits to provide the final P101 CSR including data from all immunogenicity endpoints and time-points as specified in the protocol as soon as possible post-authorisation (REC)	July 2025
Clinical	The applicant commits to submit the final CRID-001 CSR post-approval (REC)	December 2026
Clinical	The applicant committed to submit data from the co-administration studies (Study P302 Parts A and B, and Study P304) post-authorisation (REC)	March 2025
Clinical	The applicant commits to provide data from Study P303 (immunocompromised individuals and high-risk adults) post-authorisation (REC)	February 2027
Clinical	The applicant commits to provide data from Study P302 Part C (12 months revaccination) and P301 Part B (24 months revaccination), included in the RMP as a category 3 studies, post-authorisation (REC)	November 2025

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Analysis Populations

The safety and tolerability of the mRNA-1345 vaccine in adult ≥ 60 years of age is mainly based on safety data from the global, randomised, observer-blind, placebo-controlled, Phase 2/3 mRNA-1345-

P301 (P301) with supportive data from the observer-blind, placebo-controlled, Phase 1 dose-escalation study mRNA-1345-P101 (P101).

Participants were analysed according to the treatment received. The safety dataset for mRNA-1345 includes a total of 18,292 subjects in the intended treatment population of adults ≥ 60 years who received at least one dose of 50 µg mRNA-1345 (Study P301: 18,245 subjects and Study P101: 47 subjects) (Table 24)Correspondingly, 18,243 subjects received at least one dose of placebo (Study P301: 18,184 subjects and Study P101: 59 subjects). Safety data was not pooled across the two studies but presented separately.

Table 24: Number of participants exposed to 50 µg mRNA-1345 and duration of study

Study	Age group	Total Participants Exposed to Placebo	Total Participants Exposed to mRNA-1345	Follow-up After Injection (6/12 months) placebo participants	Follow-up After Injection (6/12 months) exposed participants
P301	≥60 years	18,184	18,245	17050 (93.8%)/ 2335 (12.8%)	17152 (94.0%)/ 2351 (12.9%)
P101	65 to 79 years	59	47	53 (89.8%)/ 18 (30.5%)	41 (87.2%)/ 17 (36.2%)

Source Data: Study P301 CSR Table 14.1.7.1, Study P101 CSR Table 14.1.7.2.1

In addition, 192 adults 65 to 79 years in the safety set of study P101 received at least one dose of mRNA-1345 with strengths different than 50 µg (12.5, 25, 100 and 200 µg). Furthermore, 21 adults of Japanese descent ≥60 years received at least one dose of 100 µg mRNA-1345 and 79 adults 18 to 49 years of age received at least one dose of 50, 100 or 200 µg mRNA-1345.

In study P301, the median follow-up time was 257.0 days (range: 1 to 530 days) in both the mRNA-1345 and the placebo arm. At the data cut-off date (30 April 2023), 18140 participants (99.4 %) in the mRNA-1345 and 18059 participants (99.3%) in the placebo arm had ≥28 days of safety follow-up and 17152 (94.0%) and 17050 participants (93.8%) had ≥6 months of safety follow-up, respectively. Furthermore, a Solicited Safety Set included all randomised participants who received any study injection and contributed any solicited AR data. This population was used for analyses of solicited ARs.

In study P101, the median follow-up time was 364.0 days (12 months; range: 86 to 389 days) in the age group ≥ 65 years who had received 50 µg mRNA-1345, whereof 87.2% of participants (41/47) had ≥6 months and 36.2% (17/47) had ≥12 months of safety follow-up.

In the other groups the median follow-up was 362.0 to 369.5 days in the age group ≥ 65 years (12.5, 25, 100, or 200 µg mRNA-1345) whereof 81.3% to 93.8% of participants had ≥6 months and 27.1% to 52.1% had ≥12 months of follow-up.

Demographics and other baselines

In Study P301, demographic and baseline characteristics were generally balanced between study groups.

Of the Safety Set of Study P301, 22567 participants (61.9%) were aged between 60 to 69 years, 10975 participants (30.1%) were between 70 and 79 years, while 2887 participants (7.9%) were 80 years or older. The enrolment target of 10% participants ≥80 years of age as defined in the study protocol for study P301 was consequently not achieved. The median age was 67.0 years (range: 60 to 108 years).

In the pivotal study P301, approximately 51% of the participants were male, 61.8% were White, 12% Black, 11% Asian and about 33.6% were Hispanic or Latino. As for their medical history, 7.2% had risk factors for Lower Respiratory Tract Diseases (such as CHF/COPD). Overall, 10686 participants (29.4%) had ≥1 comorbidity of interest, or conditions associated with increased risk of severe RSV disease and LRTD, which included COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease.

2.6.8.2. Adverse events

Safety assessments

Solicited AEs were collected by an eDiary through 7 days after injection and included local solicited AEs (injection site pain, erythema, swelling/induration and axillary (underarm) swelling or tenderness ipsilateral to the side of injection) and systemic solicited AEs (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills and fever). In addition, potential reactogenicity-related AEs (related AEs that matched solicited AR terms) with onset after day 7 in study P301 underwent blinded manual review to identify potential delayed-onset reactogenicity events. Solicited AEs persisting beyond day 7 after vaccination or meeting the criteria for a SAE were additionally reported and analysed as unsolicited AEs.

In both studies, any unsolicited AEs were collected up to 28 days after injection, and thereafter all SAEs, MAAEs, AESIs and AEs leading to discontinuation throughout the follow-up. In addition to predefined AESIs, the MAH conducted Standardized MedDRA Queries for including but not limited to anaphylaxis, cardiac arrhythmias, Angioedema and Hypersensitivity and Guillain-Barré Syndrome. Investigators were instructed to report any cases of suspected myocarditis and pericarditis as AESIs, which then underwent an independent blinded review by an independent Cardiac Event Adjudication Committee (CEAC) of cardiologists to determine if they met CDC criteria of "probable" or "confirmed" events.

Scheduled standard clinical laboratory tests were performed in study P101. No scheduled safety laboratory tests were performed in study P301. Due to the low probability of pregnancies occurring in the study population (≥ 60 years), pregnancy information was not collected in Study P301.

Reactogenicity

Study P301

For study P301, the solicited safety set (SSS), used to determine reactogenicity, included all randomised participants who received any IMP and contributed any solicited ARs data. It consisted of 36276 participants (18174 in the mRNA-1345 50 µg group and 18102 in the placebo group).

The reactogenicity profile for Grade 3 and Grade 4 solicited adverse reactions observed in study P301 is presented in Table 25.

Table 25: Overview of solicited adverse reactions solicited safety set

	Placebo (N=18102) n/N1 (%)	mRNA-1345 50 µg (N=18174) n/N1 (%)
Solicited Adverse Reactions within 60 Minutes after Vaccination	1178/17679 (6.7)	1195/17764 (6.7)
Grade 3 or Grade 4	52/17679 (0.3)	53/17764 (0.3)
Solicited Local Adverse Reactions within 7 Days	2939/18097 (16.2)	10591/18171 (58.3)
Grade 3 or Grade 4	310/18097 (1.7)	561/18171 (3.1)
Solicited Systemic Adverse Reactions within 7 Days	5959/18101 (32.9)	8613/18171 (47.4)
Grade 3 or Grade 4	513/18101 (2.8)	719/18171 (4.0)

N1=Number of exposed participants who submitted any data for the event.

Source: Table 14.3.1.1.1

In study P301, the mRNA-1345 group had a higher incidence and severity of solicited local and systemic adverse reactions (58.3% and 47.4%, respectively) compared to the placebo group (16.2% and 32.9%). This trend is consistent across all grades of severity, with the mRNA-1345 group showing higher percentages than the placebo group. The most frequent local adverse reaction was pain, with 55.9% of the mRNA-1345 group and 13.8% of the placebo group experiencing this reaction. Fatigue was the most frequent systemic AR, with 30.8% of the mRNA-1345 group and 20.0% of the placebo group experiencing this event. The majority of ARs were mild in severity.

Solicited ARs with severity Grade 3 or above were reported for 6.1% of participants in the mRNA-1345 group and 4.0% of participants in the placebo group. There were no Grade 4 local ARs reported. The only Grade 4 systemic AR reported was fever, defined as temperature >40.0°C (0.2% in both groups). Grade 3 Local Adverse Reactions were reported in 3.1 % of participants of the mRNA-1345 group and in 1.7% of participants in the placebo group. In the mRNA-1345 group, Grade 3 pain was reported in 1.7% of the participants. Grade 3 erythema was reported in 0.6% of the participants, and swelling (hardness) was observed in 0.9% of the participants, Axillary (Underarm) Swelling in 0,9% of the participants (Table 26).

Grade 3 solicited systemic adverse reactions were reported in 3.8% of participants in the mRNA-1345 group and 2.7% in the placebo group. The most frequently reported Grade 3 systemic event was fatigue (1.7% of participants in the mRNA-1345 group and 1.2% of participants in the placebo group), followed by headache (1.5% of participants in the mRNA-1345 group and 1.2% in the placebo group), myalgia (1.4% of participants in the mRNA-1345 group and 0.9% in the placebo group), and arthralgia (1.1% of participants in the mRNA-1345 group and 0.7% of participants in the Placebo group) (Table 22).

Onset and duration of solicited local and systemic ARs

Solicited ARs typically resolved in 1-2 days after onset. The majority of solicited local and systemic ARs occurred within 1 to 2 days after injection with a median duration of solicited local and systemic ARs of 1 to 2 days in the mRNA-1345 and placebo arm. 6.7% of subjects in the mRNA-1345 arm and 5.1% in the placebo arm had solicited ARs that persisted beyond Day 7 with fatigue (3.4% in the mRNA-1345 vs. 2.8% in the placebo arm), arthralgia (2.8% vs. 2.6%), and myalgia (2.3% vs. 2.1%) being the most frequently reported solicited ARs beyond 7 days. Potential delayed-onset reactogenicity (related unsolicited ARs matching solicited AE terms) occurred in 7 participants in the mRNA-1345 vs. 8 participants in the placebo arm. None of the cases of delayed-onset reactogenicity were considered to be severe or categorised as SAE.

The median duration for any Grade 3 or 4 solicited AR was 3.0 days in the placebo arm and 4.0 days in the mRNA-1345 arm. Among Grade 3 or 4 solicited local ARs the median duration was 1.0 days in the placebo arm and 3.0 days in the mRNA-1345 arm. Among Grade 3 or 4 solicited systemic ARs the median duration was 4.0 days in the placebo arm and 4.0 days in the mRNA -1345 arm. The Grade 3 or 4 solicited systemic ARs with the longest median duration in the mRNA-1345 arm were fatigue (4.0 days) and arthralgia (3.0 days).

Table 26: Percentages of participants with solicited local adverse reactions reported within 7 days after injection

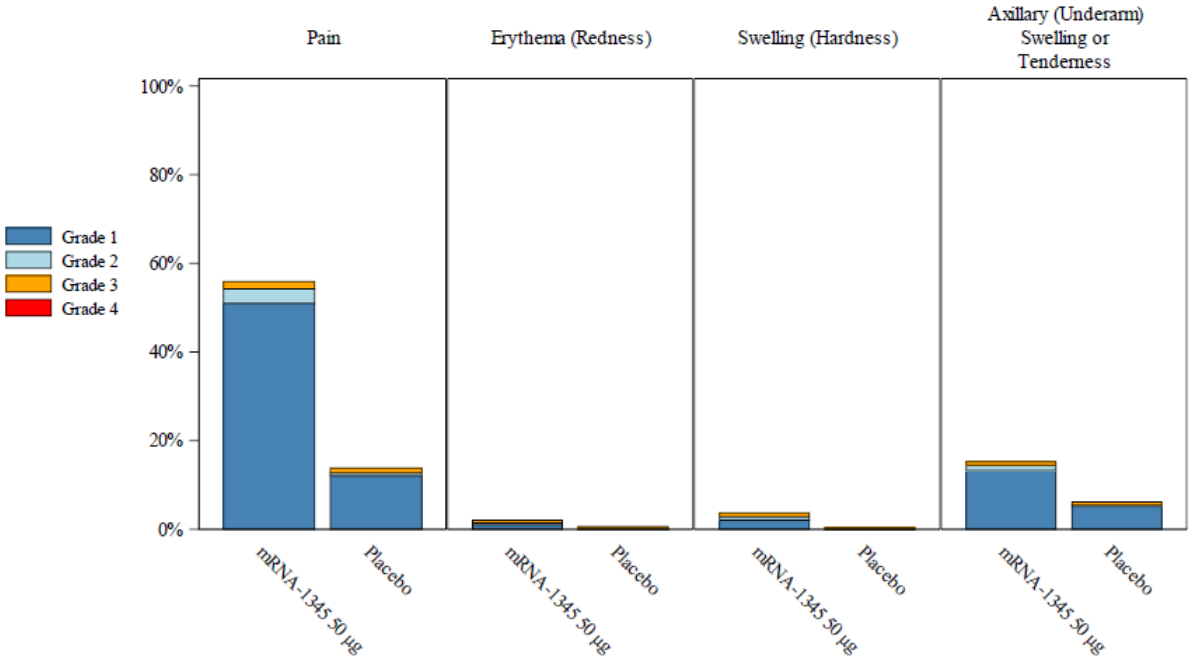
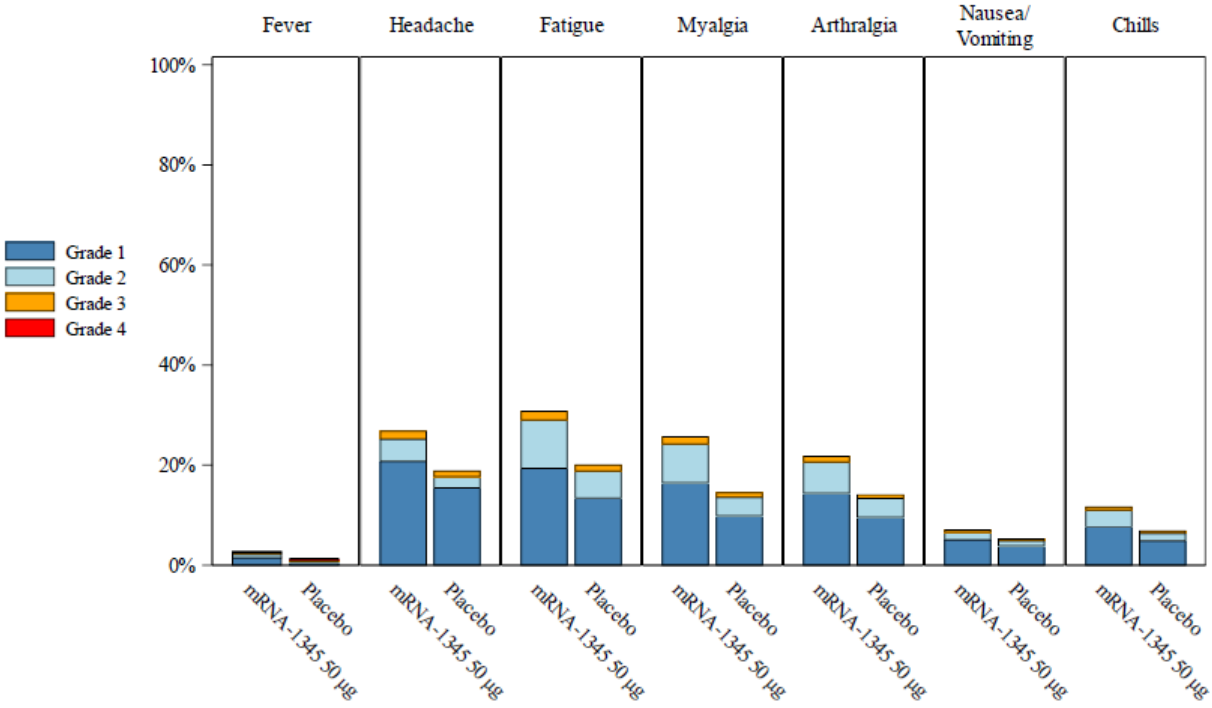


Table 27: Percentages of Participants with Solicited Systemic Adverse Reactions Reported within 7 Days after Injection



Study P101

Adults Aged 18 to 49 Years

A dose-dependent increase in local ARs was observed in 73.7% (14/19) at 50 µg, 90% (18/20) at 100 µg, and 100% (20/20) at 200 µg of mRNA-1345. The incidence of solicited systemic ARs was dose-dependent: 11/19 participants (57.9%), 14/20 participants (70.0%), and 20/20 participants (100%) in the 50 µg, 100 µg and 200 µg groups, respectively. Most Grade 3 systemic ARs were reported in the 200 µg mRNA-1345 group. No dose-dependence was observed for time to onset of solicited ARs. The severity, time to onset, and duration after subsequent injections were similar to characteristics after the first injection, in the three injections group with 100 µg.

Adults Aged 65 to 79 Years

Overall, the incidence of solicited local and systemic ARs after one injection of mRNA-1345 was lower in the 12.5 µg, 25 µg, and 50 µg groups than in the 100 µg and 200 µg mRNA-1345 groups. However, the percentage experiencing Grade 3 (severe) reactions remained relatively low across all dosage levels. No dose-dependence was observed for time to onset of solicited ARs. In the booster Injection cohort, a similar profile was seen in reactogenicity. As the dosage increased, the percentage of participants experiencing adverse reactions tended to increase, with some minor exceptions.

Japanese Descent Aged ≥60 Years

Solicited ARs were observed in 95.2% of the participants (20/21) in the 100 µg mRNA-1345 group, and in 75.0% (3/4) in the placebo group. The majority of solicited ARs were mild in severity, and none were severe. The cohort presented a similar reactogenicity profile like the other cohorts.

Overall duration across all Cohorts

The median duration of any solicited AR was 3.0 to 4.0 days in the mRNA-1345 groups and 3.0 days in the placebo group, with a trend of being a bit shorter in the older cohorts.

Unsolicited adverse events

Study P301

Within 7 days after injection the incidence of unsolicited TEAEs was 9.6% in the mRNA-1345 group versus 7.9% in the placebo group for events regardless of relationship and 5.5% versus 4.3% for events judged to be related to study vaccine. The incidence might be higher in the mRNA-1345 group due to solicited ARs with onset before Day 7 that persisted beyond Day 7 and occurrence of other events associated with reactogenicity in the mRNA-1345 group. While the mRNA-1345 vaccine group had a higher incidence of TEAEs than the placebo group, the majority of these events were non-serious.

The incidence of TEAEs within 28 days after injection (20.5% in the mRNA-1345 arm vs. 18.8% in the placebo arm, whereof 5.7% vs. 4.4% were related to the study injection) was affected by the persistence of solicited ARs beyond Day 7 (6.7% of subjects in the mRNA-1345 and 5.1% in the placebo arm) and occurrence of other events associated with reactogenicity. The incidence of TEAEs with onset 8 days after injection up to 28 days after injection was balanced between the groups (13.0% in the mRNA-1345 group versus 12.4% in the placebo group). TEAEs up to 28 days after injection were generally reported as mild (12.7% versus 11.2%) or moderate (7.2% versus 6.8%) in severity. The distribution of the severity of these adverse events was equal between both groups. Most commonly reported SOC was Infections and infestations (7.8% in the mRNA-1345 group versus 7.2% in the placebo group), with a higher incidence of COVID-19 in the mRNA-1345 group at 2.1% versus 1.8% in the placebo group. "General disorders and administration site conditions" were more frequently reported in the mRNA-1345 group (4.4%) than in the placebo group (3.3%). "fatigue "was

reported at a rate of 2.7% in the mRNA-1345 group compared to 2.2% in the placebo group. Adverse events like "headache" were also more frequently reported in the mRNA-1345 group (1.7%) compared to the placebo group (1.4%).

Numerical imbalances in PTs reported within 7 and within 28 days post vaccination include for instance vertigo (22 participants in the mRNA-1345 vs. 12 in the placebo arm) and Dizziness (27 vs. 23 participants). In addition, there are several imbalances in other PTs of interest, including pneumonitis (9 vs. 4 participants up to 28 days and 31 vs 11 participants up to data cut-off), respiratory symptoms (7 vs. 2 participants up to 28 days), Seborrhoeic dermatitis (3 vs. 1 participants up to 28 days and 7 vs. 1 participants up to data cut-off) and Trigger finger (4 vs. 0 participants up to 28 days and 20 vs. 9 participants reporting MAAEs up to data cut-off).

Related unsolicited adverse events

When looking at treatment related TEAES, 4.4% in the placebo group reported adverse events compared to 5.7% in the mRNA-1345 group. Notable differences in reported TEAEs included headaches (1.1% in placebo vs 1.3% in mRNA-1345), vomiting (0.2% vs 0.3%), arthralgia (1.9% vs 2.0%), fatigue (2.2% vs 2.6%), and injection site pain (0.3% vs 0.7%). In addition, there are numerical imbalances in the related TEAEs reported for some PTs including dizziness (7 related cases for mRNA-1345 vs. 1 for the placebo), hypertension (16 vs. 10), injection site pruritus (4 vs. 1) and rash (4 vs. 1).

Table 28: Overall summary of unsolicited TEAEs after injection safety set in study P301

Overall Summary of Unsolicited TEAEs up to 7 Days After Injection
Safety Set

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs Regardless of Relationship to Study Vaccination		
All	1439 (7.9)	1743 (9.6)
Serious	26 (0.1)	27 (0.1)
Fatal	1 (<0.1)	0
Medically-Attended	416 (2.3)	468 (2.6)
Leading to Study Discontinuation	2 (<0.1)	1 (<0.1)
Severe/>=Grade 3	73 (0.4)	70 (0.4)
Non-Serious [1]	1413 (7.8)	1716 (9.4)
Severe/>=Grade 3 [1]	60 (0.3)	58 (0.3)
At Least 1 Non-Serious Event [2]	1418 (7.8)	1723 (9.4)
Severe/>=Grade 3 [2]	60 (0.3)	60 (0.3)
Any AESI	2 (<0.1)	1 (<0.1)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs Related to Study Vaccination		
All	776 (4.3)	1007 (5.5)
Serious	2 (<0.1)	3 (<0.1)
Fatal	0	0
Medically-Attended	43 (0.2)	56 (0.3)
Leading to Study Discontinuation	0	1 (<0.1)
Severe/>=Grade 3	51 (0.3)	53 (0.3)
Non-Serious [1]	774 (4.3)	1004 (5.5)
Severe/>=Grade 3 [1]	49 (0.3)	51 (0.3)
At Least 1 Non-Serious Event [2]	774 (4.3)	1006 (5.5)
Severe/>=Grade 3 [2]	49 (0.3)	52 (0.3)
Any AESI	1 (<0.1)	1 (<0.1)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs up to 28 Days after Vaccination, Regardless of Relationship to Study Vaccination		
All	3412 (18.8)	3749 (20.5)
Serious	111 (0.6)	115 (0.6)
Fatal	6 (<0.1)	1 (<0.1)
Medically-Attended	1531 (8.4)	1606 (8.8)
Leading to Study Discontinuation	11 (<0.1)	2 (<0.1)
Severe/>=Grade 3	135 (0.7)	129 (0.7)
Non-Serious [1]	3301 (18.2)	3634 (19.9)
Severe/>=Grade 3 [1]	72 (0.4)	63 (0.3)
At Least 1 Non-Serious Event [2]	3348 (18.4)	3691 (20.2)
Severe/>=Grade 3 [2]	73 (0.4)	72 (0.4)
Any AESI	8 (<0.1)	3 (<0.1)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs up to 28 Days after Vaccination, Related to Study Vaccination		
All	795 (4.4)	1035 (5.7)
Serious	3 (<0.1)	4 (<0.1)
Fatal	0	0
Medically-Attended	51 (0.3)	66 (0.4)
Leading to Study Discontinuation	0	1 (<0.1)
Severe/>=Grade 3	52 (0.3)	53 (0.3)
Non-Serious [1]	792 (4.4)	1031 (5.7)
Severe/>=Grade 3 [1]	50 (0.3)	51 (0.3)
At Least 1 Non-Serious Event [2]	792 (4.4)	1034 (5.7)
Severe/>=Grade 3 [2]	50 (0.3)	52 (0.3)
Any AESI	1 (<0.1)	1 (<0.1)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs up to Data Cutoff Date (30APR2023), Regardless of Relationship to Study Vaccination		
Serious	1092 (6.0)	1114 (6.1)
Fatal	83 (0.5)	84 (0.5)
Medically-Attended	6923 (38.1)	7145 (39.2)
Leading to Study Discontinuation	105 (0.6)	99 (0.5)
Any AESI	35 (0.2)	37 (0.2)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs up to Data Cutoff Date (30APR2023), Related to Study Vaccination		
Serious	5 (<0.1)	4 (<0.1)
Fatal	0	0
Medically-Attended	60 (0.3)	85 (0.5)
Leading to Study Discontinuation	0	1 (<0.1)
Any AESI	2 (<0.1)	2 (<0.1)

[1] Participants who did not report any serious TEAE are included in the summary of 'non-serious' and 'severe/>=Grade 3 non-serious'.

[2] Participants with at least one non-serious TEAE are included.

Study P101 (65-79 years)

After the first injection, unsolicited AEs were reported by 66.7%, 50%, 63.8%, 41.7%, and 60.4% of participants in the 12.5, 25, 50, 100, and 200 µg mRNA-1345 group, respectively and in 35.6% of participants in the placebo group. The group sizes in study P101 were small and no clear trend regarding a possible dose effect on the frequency of unsolicited AEs were detectable.

Related unsolicited adverse events

No clear dose-dependent trend in the incidence of reported related TEAEs was evident and most of the related TEAEs were associated with reactogenicity. In addition, two related TEAEs of dizziness (100 and 200 µg group) and aTTP prolonged (12.5 µg and 200 µg), one related TEAE of diarrhoea (25 µg), alanine aminotransferase increased (25 µg), Aspartate aminotransferase increased (25 µg) and pain in

extremity (100 µg) were reported. PTs with related unsolicited AEs for the 50-µg group were 1 case of hypertension and Prothrombin time prolonged.

For the younger age cohort, the groups were small (20 or less) and in the 50-µg group 2 related cases of injection site pain were reported. Other reported PTs were 1 case of arthralgia (100 µg), injection site induration (100 µg), injection site pruritus (200 µg), and musculoskeletal stiffness (200 µg).

Severe Adverse Events

Study P301

Table 29: Participant incidence of unsolicited severe (severe/≥grade 3) TEAEs up to 28 Days after injection – preferred terms reported in ≥2 participants overall (safety set)

Preferred Term	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Number of Participants Reporting Unsolicited Severe/≥Grade 3 TEAEs	135 (0.7)	129 (0.7)
Number of Unsolicited Severe/≥Grade 3 TEAEs	171	172
Fatigue	27 (0.1)	28 (0.1)
Arthralgia	17 (<0.1)	13 (<0.1)
Headache	9 (<0.1)	12 (<0.1)
Myalgia	14 (<0.1)	11 (<0.1)
Hypertension	5 (<0.1)	6 (<0.1)
Chronic obstructive pulmonary disease	5 (<0.1)	4 (<0.1)

Injection site pain	1 (<0.1)	4 (<0.1)
Pneumonia	3 (<0.1)	4 (<0.1)
Acute myocardial infarction	3 (<0.1)	3 (<0.1)
Chills	0	3 (<0.1)
Dehydration	1 (<0.1)	3 (<0.1)
Injection site erythema	0	3 (<0.1)
Acute kidney injury	1 (<0.1)	2 (<0.1)
Blood pressure increased	4 (<0.1)	2 (<0.1)
Cholecystitis acute	1 (<0.1)	2 (<0.1)
Coronary artery disease	0	2 (<0.1)
Osteoarthritis	1 (<0.1)	2 (<0.1)
Prostate cancer	0	2 (<0.1)
Pyelonephritis	0	2 (<0.1)
Syncope	0	2 (<0.1)
Myocardial infarction	2 (<0.1)	1 (<0.1)
Non-cardiac chest pain	2 (<0.1)	1 (<0.1)
Immunization stress-related response	3 (<0.1)	0
Asthma	2 (<0.1)	0
Ischemic stroke	2 (<0.1)	0
Seizure	2 (<0.1)	0

Abbreviations: AR = adverse reaction; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
A TEAE was defined as any event not present before exposure to study injection or any event already present that worsened in intensity or frequency after exposure.
Severe TEAEs included both unsolicited severe TEAEs and ≥Grade 3 solicited ARs that met SAE criteria or lasted beyond 7 days after injection.
Percentages were based on the number of participants in the Safety Set.
Adverse events were coded using MedDRA, version 25.0.

Within 28 days post vaccination, at least one severe/≥Grade 3 TEAE was reported in 0.7% of participants in both the mRNA-1345 and placebo groups (129 and 135 participants, respectively). The most frequently reported severe/≥Grade 3 events in the mRNA1345 vs. placebo arm were fatigue, arthralgia, headache, and myalgia (all reported by 0.1% or less in both groups). The only clear imbalances seen regarding severity ≥Grade 3 is injection site erythema reported by 3 participants in the mRNA-1345 arm vs. 0 participants in the placebo arm, chills (3 vs.0), injection site pain (4 vs 1). Severe TEAEs related to the study injection were observed in 0.3% of participants in both groups. Most of these events were associated with reactogenicity: For the SOC "General disorders and administration site conditions," the mRNA-1345 group had 39 participants (0.2%) reporting adverse events, while the placebo group had 28 participants (0.2%). Under "Musculoskeletal and connective tissue disorders," 15 participants (<0.1%) from the mRNA-1345 group and 24 participants (0.1%) from the placebo group experienced adverse events. For the SOC "Nervous System Disorders," the mRNA-1345 group reported 11events (<0.1%) against the placebo group 10 (<0.1%).

Study P101

Adults Aged 18 to 49 Years:

No adverse events of Grade 3 or higher were reported in this age group.

Adults 65 to 79 Years

No dose-dependent trends were observed across the mRNA-1345 dose groups in the incidence of unsolicited TEAEs reported as severe/Grade ≥3: 12.5% (6/48), 6.3% (3/48), 10.6% (5/47), 8.3% (4/48), and 6.3% (3/48) of participants in the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg mRNA-1345 groups and 0 participants in the placebo group. No event PT was reported as severe/Grade ≥3 for more than 1 participant.

At least 1 unsolicited TEAE of Grade 3 or higher judged by the investigator to be related to the study vaccination was reported in a total of 2 /239 (0.8%) participants in the mRNA-1345 group. The specific AEs were prolonged prothrombin time and hypertension, both reported by 2/47 participants (4.3%) in the mRNA-1345 50 µg group.

Japanese Descent Aged ≥60 Years:

Only one adverse event of Grade 3 or higher was reported in the mRNA-1345 group. It was judged as non-related by the investigator.

MAAEs

Study P301

MAAEs, excluding Per-protocol Illness Visits, were reported slightly more frequently in the mRNA-1345 group (8.8%; 2020 participants) than in the placebo arm (8.4%; 1881 participants) up to 28 days after injection and up to data cut-off (39.2% vs. 38.1%). The most common MAAEs over a 28-day period were infections and infestations. For the mRNA-1345 group, the rate was 3.7% over 28 days and 19.9% up to the data cut-off. For the placebo group, the rate was 3.2% over 28 days and 19.1% up to the data cutoff. Up to the data cut-off, there are numerical imbalances for the PT of Hypercholesterolaemia (113 participants in the mRNA-1345 vs. 93 in the placebo arm).

Related MAAEs excluding Per-protocol Illness Visits, up to 28 days post-injection were slightly higher in the mRNA group with 66 participants (0.4%) reporting 90 events, compared to 51 participants (0.3%) in the placebo group reporting 57 events. Events in the SOCs "General disorders and administration site conditions" were the most frequent (9 (<0.1%) placebo vs. 19 (0.1%) mRNA-1345 group). The mRNA-1345 group also saw a higher incidence in SOCs like "nervous system disorders" (10 vs. 7 events) and "skin disorders" (8 vs. 2 events). In addition, there were 4 MAAEs of vomiting in the mRNA-1345 vs. 1 in the placebo arm that were evaluated to be related to vaccination. In total 58 related TEAEs of vomiting and 3 related TEAEs of nausea were reported in the mRNA-1345 arm up to 28 days.

Up to data-cut off, in the mRNA-1345 group, 85 (0.5%) participants reported 113 events, meanwhile in the placebo group 60 participants (0.43%) reported 68 MAAEs. Notably, the mRNA-1345 group had 10 (<0,1%) "vascular disorder" related events versus 7 in the placebo group and saw a higher incidence in SOCs like "nervous system disorders" (11 events vs. 9) and "skin disorders" (9 events vs. 3). However, both groups had similar overall percentages of participants reporting treatment-related MAAEs.

Study P101

Adults Aged 18 to 49 Years:

After a single injection, 9/20 (45.0%) of those given 200 µg mRNA-1345 and 4/15 (26.7%) placebo recipients reported MAAEs. Dyspnoea was noted in 2/20 participants 3.4% of the mRNA-1345 group,

but only after 28 days post-injection. None of the MAAEs were judged by the investigator to be related to IMP and no MAAEs were reported in the other dose groups.

In the booster group, MAAEs were recorded in 2/20 (10%) participants after the first injection, 1/16 (6.3%) after the second, and 2/15 (13.3%) after the third. Notably, 2 incidences of palpitations were reported but considered to be unrelated to the IMP. No MAAEs in the placebo group were reported.

Adults Aged 65 to 79 Years:

MAAEs varied across doses, with 64.6% (31/48), 50.0% (24/48), 59.6% (28/47), 33.3% (16/48), and 56.3% (27/48) of participants in the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg mRNA 1345 groups, respectively and 35.6% (21/59) of participants in the placebo group. Common AEs included COVID-19, hypertension, arthralgia, back pain, osteoarthritis, and urinary tract infections.

Japanese Descent Aged ≥60 Years:

1/21 (4.8%) of those receiving mRNA-1345 reported 2 MAAEs. The participant experienced diplopia, and an intracranial aneurysm, all deemed unrelated to the vaccine. One placebo recipient had vertigo post-injection.

Adverse events of special interest and SMQs:

Study P301

Up to 28 days after vaccination, 3 participants in the mRNA-1345 vs. 8 in the placebo arm (<0.1% for each group) in study P301 reported AESIs and up to the data cut-off 37 vs. 35 participants (0.2% for each group) reported AESIs (Table 30).

Table 30: Participant incidence of unsolicited TEAEs of special interest as assessed by investigator by SOC and PT (safety set)

	Placebo (N=18184)		mRNA-1345 50 µg (N=18245)	
System Organ Class Preferred Term	Events	Participants n (%)	Events	Participants n (%)
AESIs up to **7 days** after injection	2	2 (<0.1)	1	1 (<0.1)
Nervous system disorders	2	2 (<0.1)	1	1 (<0.1)
Facial paralysis	0	0	1	1 (<0.1)
Seizure	2	2 (<0.1)	0	0

AESIs up to **28 days** after injection (includes up to 7 days)	8	8 (<0.1)	3	3 (<0.1)
Blood and lymphatic system disorders	2	2 (<0.1)	0	0
Thrombocytopenia	2	2 (<0.1)	0	0
Immune system disorders	0	0	1	1 (<0.1)
Anaphylactic reaction	0	0	1	1 (<0.1)
Nervous system disorders	5	5 (<0.1)	2	2 (<0.1)
Bell's palsy	2	2 (<0.1)	1	1 (<0.1)
Facial paralysis	0	0	1	1 (<0.1)
Seizure	3	3 (<0.1)	0	0
Cardiac disorders	1	1 (<0.1)	0	0
Pericarditis	1	1 (<0.1)	0	0

AESIs up to **data cutoff** date (includes up to 28 days)	37	35 (0.2)	39	37 (0.2)
Infections and infestations	1	1 (<0.1)	0	0
Herpes zoster oticus	1	1 (<0.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (<0.1)	0	0
Myelodysplastic syndrome	1	1 (<0.1)	0	0
Blood and lymphatic system disorders	15	15 (<0.1)	9	9 (<0.1)
Thrombocytopenia	13	13 (<0.1)	9	9 (<0.1)
Immune thrombocytopenia	1	1 (<0.1)	0	0
Pancytopenia	1	1 (<0.1)	0	0
Immune system disorders	0	0	1	1 (<0.1)
Anaphylactic reaction	0	0	1	1 (<0.1)
Nervous system disorders	17	15 (<0.1)	23	22 (0.1)
Bell's palsy	3	3 (<0.1)	6	6 (<0.1)
Seizure	7	6 (<0.1)	5	5 (<0.1)
Facial paralysis	2	2 (<0.1)	3	3 (<0.1)
Generalized tonic-clonic seizure	0	0	2	2 (<0.1)
Cerebrovascular accident	0	0	1	1 (<0.1)
Encephalopathy	0	0	1	1 (<0.1)
Epilepsy	2	2 (<0.1)	1	1 (<0.1)
Essential tremor	0	0	1	1 (<0.1)

Myasthenia gravis	0	0	1	1 (<0.1)
Petit mal epilepsy	0	0	1	1 (<0.1)
Seizure like phenomena	0	0	1	1 (<0.1)
Alcoholic seizure	2	2 (<0.1)	0	0
Status epilepticus	1	1 (<0.1)	0	0
Cardiac disorders	2	2 (<0.1)	5	4 (<0.1)
Pericarditis	1	1 (<0.1)	3	2 (<0.1)
Atrial fibrillation	0	0	1	1 (<0.1)
Myocarditis	0	0	1	1 (<0.1)
Cardiac tamponade	1	1 (<0.1)	0	0
Congenital, familial and genetic disorders	1	1 (<0.1)	0	0
Myotonic dystrophy	1	1 (<0.1)	0	0
Investigations	0	0	1	1 (<0.1)
Platelet count decreased	0	0	1	1 (<0.1)

Abbreviations: AESI=adverse event of special interest; MedDRA: Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
A TEAE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Percentages were based on the number of participants in the Safety Set.
Adverse events were coded using MedDRA, version 25.0.

Myocarditis and pericarditis

Up to 7 days after injection, no AESIs of myocarditis or pericarditis were reported in study P301 and up to 28 days after injection, one AESI of pericarditis was reported in the placebo arm with onset on Day 8. This case was adjudicated by the CEAC as not a charter-defined event. This was the only AESI of myocarditis or pericarditis that was reported within the 42-day risk window as defined by the applicant.

Up to data cutoff, one AESI of myocarditis (onset on Day 62) and 3 AESIs of pericarditis in 2 participants (onset on Days 48 and 223 for one participant and on Day 81 for another participant) were reported in the mRNA-1345 arm. The CEAC adjudicated the 3 AESIs of pericarditis as acute pericarditis and the one AESI of myocarditis as not a charter-defined event. None of the cases were evaluated to be related to study injection.

In addition, one TEAE of myocarditis (verbatim: non-sustained cardiac arrhythmia potential myocarditis) was retrieved by the SMQ search. This event was adjudicated by the CEAC as not a charter-defined event.

Cardiac arrhythmias

Up to 7 days after injection, the number of participants reporting AEs in the HLGT "Cardiac arrhythmias" was numerically imbalanced between the mRNA-1345 and the placebo arm (11 participants in the mRNA-1345 vs. 8 in the placebo arm) with Tachycardia (4 vs. 1), Bradycardia (3 vs. 1) and Atrial fibrillation (0 vs. 4) showing imbalances. Up to 28 days after injection, 34 participants in the mRNA-1345 vs. 27 in the placebo group reported AEs within the HGLT "Cardiac arrhythmias" including tachycardia (7 vs. 3), atrial fibrillation (9 vs. 11) and Bradycardia (4 vs. 2). One AE of tachycardia, one AE of palpitations and one AE of atrial fibrillation in the mRNA-1345 arm and 2 AEs of atrial fibrillation in the placebo arm were considered related to the study injection.

The review of the narrow/broad SMQs for cardiac arrhythmias identified AEs in 17 participants in the mRNA-1345 vs. 10 in the placebo arm up to 7 days and in 45 vs. 41 participants up to 28 days after injection. Within 7 days numerical imbalances were seen on PT level including for syncope (4 vs. 0) and tachycardia (4 vs. 1) and up to 28 days for tachycardia (7 vs. 3) and bradycardia (4 vs. 2).

New onset or worsening of neurological conditions

Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM)

No AESIs of GBS and ADEM were reported up to the data cut-off. Using narrow/broad scope SMQ searches for GBS, events related to GBS were identified in a total of 10 participants in the mRNA-1345 vs. 5 in the placebo arm within 7 days and 34 vs. 28 participants (35 vs. 28 events) up to 28 days after vaccination. Identified events up to 28 days included cases of Asthenia (13 vs. 11 events), Hypoesthesia (5 vs. 1 event) and Paraesthesia (4 vs. 8 events). In the mRNA-1345 arm one TEAE of facial paralysis and of hypoesthesia was considered related to the study vaccination per investigators.

Seizure

Seizure or related event AESIs were reported for 10 participants in the mRNA-1345 group and 11 participants in the placebo group up to data cutoff. One participant in the placebo arm experienced an event of seizure on Day 1 that was considered to be related to the study injection per investigator. All other events were considered unrelated to study injection.

Bell's palsy/facial paralysis

In Study P301, the number of reported AESIs of Bell's palsy/facial paralysis were balanced between the mRNA-1345 and placebo groups (2 participants in each group) using a 42-day risk window.

One event of facial paralysis was considered related to study injection by the investigator. This event was reported with onset on Day 5 after mRNA-1345 injection, was considered serious, and occurred in a participant with a medical history of hypertension.

Up to the data cut-off, a total of 6 participants in the mRNA-1345 group and 3 participants in the placebo group had a reported AESI of Bell's palsy, all with risk factors for Bell's palsy noted in their medical history. A total of 3 participants in the mRNA-1345 group and 2 participants in the placebo group reported AESIs of facial paralysis.

Anaphylactic reaction

In total, one AESI of anaphylactic reaction was reported in the mRNA-1345 up to the data cut-off, which was considered unrelated to the study vaccination (a 67-year-old male participant reported anaphylactic reaction to bee venom on Day 28 that resolved on Day 29). On Day 11, a participant in the mRNA-1345 group experienced a SAE of anaphylactic reaction, which was not classified as an AESI. The anaphylactic reaction was due to an insect sting. Events of anaphylactic reaction were identified by SMQ searches in 4 participants in the mRNA-1345 arm and 5 participants in the placebo arm, up to data cutoff. All cases up to data cutoff were considered unrelated to the study injection.

Angioedema and hypersensitivity

The incidence of events within the angioedema and hypersensitivity SMQs (narrow and narrow/broad) was higher in the mRNA-1345 group than the placebo group up to 7 days after injection, up to 28 days after injection, and up to the data cut-off. This was driven by events of urticaria following mRNA-1345 immunisation for both SMQs. Up to 28 days after injection, no events were reported with a PT of

angioedema. For the Hypersensitivity narrow/broad scope SMQ 179 (1.0%) events were reported for mRNA-1345 vs 162 (0.9%) for placebo, up to 28 days after injection. Up to data cutoff, 625 (3.4%) participants in the mRNA-1345 group and 551 (3.0%) participants in the placebo group were identified.

Urticaria

The PT Urticaria were more frequently reported in mRNA-1345 (15 vs. 5 in the placebo arm up to 28 days after injection and 48 vs 38 up to data cut-off) and none were reported as serious. Urticaria was related to study injection for 6 participants in the mRNA-1345 group versus 1 participant in the placebo group, and the onset ranged between days 1-17 after vaccination. Additionally, in the first 28 days post injection 1 participant in the mRNA-1345 arm reported an event of chronic urticaria (Day 20 to 271) and 1 participant in the placebo arm an event of papular urticaria (Day 27 to 93) that were considered to be unrelated to study injection by the investigator. Until data cut-off, nine participants in the mRNA-1345 group experienced 10 events of chronic urticaria, compared to 10 participants in the placebo group.

There was no clear pattern in the time to onset, duration, or localisation of urticaria. Given the lack of alternate aetiologies identified and the imbalance in reported cases the applicant included urticaria as an adverse reaction to mRNA-1345 administration in 4.8 in the SmPC.

Postmenopausal bleeding

Up to the data cut-off, in total 10 participants (10 events) in the mRNA-1345 group and 4 participants (4 events) in the placebo arm reported postmenopausal bleeding related events (vaginal haemorrhage, Postmenopausal haemorrhage, intermenstrual bleeding and abnormal uterine bleeding), whereof none were evaluated to be related by the investigator.

Up to 28 days after vaccination, 2 participants in the mRNA-1345 and 1 participant in the placebo arm reported non-serious AEs of vaginal haemorrhage. Three cases of medically attended postmenopausal haemorrhage and 2 cases of intermenstrual bleeding were reported in the mRNA-1345 arm up to the data cut-off. One serious event of postmenopausal haemorrhage was reported 153 days following administration of mRNA-1345.

Other SMQs

Other narrow and narrow/broad SMQ analyses were conducted for cardiomyopathy, cardiac failure, peripheral neuropathy, demyelination, immune-mediated/autoimmune disorders, embolic and thrombotic events, ischemic heart disease, central nervous system vascular disorders, convulsions, vasculitis and haematopoietic cytopenias including thrombocytopenia.

For the narrow/broad SMQ immune-mediated/autoimmune disorders there were identified slightly more AEs in the mRNA-1345 arm (37 events in 36 participants) than in the placebo arm (26 events in 26 participants) up to 28 days. In the mRNA-1345 arm cases of polymyalgia rheumatica, right breast dermatitis and non-urticarial dermatitis were considered to be related to the study vaccination. In addition, one case of acute dermatitis and one case of palpable purpura were considered related in the placebo arm. Up to the data cutoff, the narrow/broad scope SMQ for immune-mediated/autoimmune disorders identified 252 participants (1.4%) in the mRNA-1345 group and 228 participants (1.3%) in the placebo group with events.

Study P101

No AESIs occurred in this trial.

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs

Study P301

Within 7 days post-injection, 0.1% of participants in both the mRNA-1345 group (27 participants, 30 events) and placebo group (26 participants, 33 events) reported SAEs.

By 28 days, SAEs were reported in 0.6% of participants in both groups

Table 31 The mRNA-1345 group showed a slightly higher incidence of serious events, primarily driven by increased cases in the SOC "Infections and infestations", "Metabolism and nutrition disorders" and "Vascular disorders".

At the data cutoff, 6.1% of participants in the mRNA-1345 group and 6.0% in the placebo group experienced SAEs. Specifically, 1114 participants in the mRNA-1345 group (1634 events) and 1092 participants in the placebo group (1630 events) experienced SAEs.

Table 31: Participant incidence of serious TEAEs Regardless of causality up to 28 days after injection by SOC and PT – PTs reported for ≥2 participants in either group (safety set)

System Organ Class Preferred Term	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Number of Participants Reporting Serious TEAEs	111 (0.6)	115 (0.6)

Number of Serious TEAEs	141	136
Infections and infestations	10 (<0.1)	26 (0.1)
Pneumonia	3 (<0.1)	6 (<0.1)
Gastroenteritis	0	2 (<0.1)
Influenza	0	2 (<0.1)
Pyelonephritis	0	2 (<0.1)
Respiratory tract infection	0	2 (<0.1)
Urinary tract infection	1 (<0.1)	2 (<0.1)
Cellulitis	2 (<0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (<0.1)	14 (<0.1)
Malignant melanoma	1 (<0.1)	2 (<0.1)
Breast cancer	2 (<0.1)	1 (<0.1)
Blood and lymphatic system disorders	2 (<0.1)	0
Anemia	2 (<0.1)	0
Immune system disorders	1 (<0.1)	2 (<0.1)
Anaphylactic reaction	0	2 (<0.1)
Metabolism and nutrition disorders	2 (<0.1)	8 (<0.1)
Dehydration	0	3 (<0.1)
Hyperglycemia	0	2 (<0.1)
Nervous system disorders	12 (<0.1)	6 (<0.1)
Syncope	0	2 (<0.1)
Cerebrovascular accident	3 (<0.1)	0
Ischemic stroke	5 (<0.1)	0
Seizure	2 (<0.1)	0
Cardiac disorders	17 (<0.1)	14 (<0.1)
Acute myocardial infarction	3 (<0.1)	3 (<0.1)
Coronary artery disease	0	2 (<0.1)
Atrial fibrillation	4 (<0.1)	1 (<0.1)
Cardiac failure congestive	3 (<0.1)	1 (<0.1)

Myocardial infarction	2 (<0.1)	1 (<0.1)
Vascular disorders	5 (<0.1)	8 (<0.1)
Hypertension	1 (<0.1)	4 (<0.1)
Respiratory, thoracic and mediastinal disorders	11 (<0.1)	12 (<0.1)
Chronic obstructive pulmonary disease	7 (<0.1)	8 (<0.1)
Gastrointestinal disorders	10 (<0.1)	13 (<0.1)
Peptic ulcer	0	2 (<0.1)
Hepatobiliary disorders	3 (<0.1)	3 (<0.1)
Cholecystitis acute	1 (<0.1)	2 (<0.1)
Musculoskeletal and connective tissue disorders	6 (<0.1)	5 (<0.1)
Osteoarthritis	2 (<0.1)	1 (<0.1)
Renal and urinary disorders	5 (<0.1)	4 (<0.1)
Nephrolithiasis	1 (<0.1)	2 (<0.1)
General disorders and administration site conditions	6 (<0.1)	2 (<0.1)
Non-cardiac chest pain	3 (<0.1)	0
Injury, poisoning and procedural complications	14 (<0.1)	9 (<0.1)
Femur fracture	1 (<0.1)	2 (<0.1)
Humerus fracture	2 (<0.1)	1 (<0.1)
Wrist fracture	2 (<0.1)	0

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
A TEAE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Percentages were based on the number of participants in the Safety Set.
Adverse events were coded using MedDRA, version 25.0.

Related SAEs up to the data cutoff were reported in 4 (<0.1%) participants from the mRNA-1345 group and in 5 (<0.1%) participants from the placebo group (Table 32).

Table 32: Participant incidence of serious treatment-related TEAEs up to Data cutoff date (30APR2023) by system organ class and preferred term

System Organ Class Preferred Term	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Number of Participants Reporting Serious Treatment-Related TEAEs	5 (<0.1)	4 (<0.1)
Number of Serious Treatment-Related TEAEs	5	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0
Myelodysplastic syndrome	1 (<0.1)	0
Metabolism and nutrition disorders	0	1 (<0.1)
Dehydration	0	1 (<0.1)
Nervous system disorders	2 (<0.1)	1 (<0.1)
Facial paralysis	0	1 (<0.1)
Seizure	1 (<0.1)	0
Transient ischaemic attack	1 (<0.1)	0
Vascular disorders	0	1 (<0.1)
Superficial vein thrombosis	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	0
Chronic obstructive pulmonary disease	1 (<0.1)	0
General disorders and administration site conditions	1 (<0.1)	1 (<0.1)
Chills	0	1 (<0.1)
Pyrexia	1 (<0.1)	0

Study P101

In participants 65 to 79 years of age after the first injection and up to the booster injection or EOS 6/48 (12.5%), 3/48 (6.3%), 4/47 (8.5%), 0/48, and 1/48 (2.1%) of participants in the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg mRNA-1345 groups, respectively and 1/59 (1.7%) participants in the placebo group experienced at least one SAE. Other than 2 participants in the 12.5 µg group (2/239, 0.8%) with SAEs of pneumonia, none of the SAEs was reported by more than 1 participant and none were considered by the investigator as causally related.

In participants 65 to 79 years of age receiving a booster injection SAEs were reported for 3/99 participants (3.0%) in the mRNA-1345/mRNA-1345 group, 4/96 participants (4.2%) in the mRNA-1345/placebo total group, and 1/52 participants (1.9%) in the placebo/placebo group.

In participants 18 to 49 years of age and participants of Japanese descent aged ≥60 years no SAEs up to EOS were reported.

Deaths

Study P301

Up to data cut-off date, fatal TEAEs were reported in 84 (0.5%) participants in the mRNA 1345 group and 83 (0.5%) in the placebo group. Overall, incidence of fatal events was balanced between the mRNA-1345 and placebo groups and none of the fatal events were judged to be related to the vaccination by the investigator. There was one fatal case in the mRNA-1345 group that occurred within 28 days after vaccination (bronchial aspiration on day 21 after vaccination). None of the deaths were considered related to study injection by the investigator.

Table 33: Summary of deaths (safety set)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Total Number of Deaths Due to Any Cause, n (%)	83 (0.5)	84 (0.5)
Time of Death from the Injection (Days) [1]		
Mean (SD)	148.7 (78.16)	173.0 (88.09)
Median	144.0	178.0
Min, Max	6, 324	21, 448
Time of Death from the Injection [1], n (%)		
< 28 Days Since Injection	5 (<0.1)	1 (<0.1)
>= 28 Days to < 6 Months Since Injection	50 (0.3)	45 (0.2)
>= 6 Months to < 12 Months Since Injection	28 (0.2)	35 (0.2)
>= 12 Months to < 18 Months Since Injection	0	3 (<0.1)
>= 18 Months to < 24 Months Since Injection	0	0
>= 24 Months Since Injection	0	0

Study P101

In the group for adults 65 to 79 years, among participants receiving mRNA-1345 booster, two fatalities were reported: one due to bone sarcoma (receiving mRNA-1345 12.5 µg/placebo) and another from a road traffic accident (receiving mRNA-1345 25 µg/placebo). Both events were deemed unrelated to the study injection by investigators. No deaths were reported in the other dose groups in this age group.

For adults aged 18-49 and adults of Japanese descent aged ≥60 years, no deaths were reported.

2.6.8.4. Laboratory findings

The clinical laboratory evaluations were only done in the study P101.

Overall, there was a higher incidence of TEAEs reported for PTs associated with laboratory tests in the mRNA-1345 groups than placebo group (SOC investigations: 14 (5.9%) vs. 0 participants). These TEAEs were reported in a single participant each with the exception of activated partial thromboplastin time (aPTT) prolonged which was reported by one participant in the 12.5 µg arm and one in the 200 µg group, both evaluated to be related by investigator. In addition, one case of prothrombin time (PT) prolonged was reported after the first vaccination in the 50 µg group and evaluated to be related by investigator.

In the age cohort 18-49 one participant in the single injection 100 µg mRNA-1345 group had a TEAE of aPTT prolonged lasting from Day 10 to Day 29 and one participant in the 3-injection 100 µg mRNA-1345 group had an MAAE of WBC count increased from Day 6 to Day 24 (after Dose 3) and a TEAE of aPTT prolonged from Day 29 to Day 46 (after Dose 3). All of these laboratory events were mild, nonserious, and unrelated to study vaccine per investigator. One participant of Japanese descent had a Grade 4 high prothrombin time on Day 29 which as evaluated as not related by investigator.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Age

Incidence of solicited ARs decreased with increasing age: In the mRNA group, 61.2% of participants 60 to 69 years of age, 55.4% of participants 70 to 79 years of age; 46.3% of participants ≥80 years of

age for local solicited ARs and 48.8% of participants 60 to 69 years of age; 46.4% of participants 70 to 79 years of age; 40.1% of participants ≥80 years of age for systemic solicited ARs.

The occurrence of unsolicited TEAEs in the mRNA-1345 group was 20.4% for participants aged 60 to 69 years, 21.5% for participants aged 70 to 79 years, and 17.8% for participants aged 80 years or older. In the mRNA 1345 group, the occurrence of SAEs increased with age. The percentage of participants who experienced SAEs was 5.2% for those aged 60 to 69, 7.4% for those aged 70 to 79, and 8.4% for those aged 80 or older. The safety information stratified by age group is shown in Table 34.

Table 34: Summary of unsolicited AEs up to data cutoff date (30Apr2023) by age groups

MedDRA Terms	Age 60-64		Age 65-74		Age 75-84		Age 85+	
	mRNA-1345 N=6183 n (%)	Placebo N=6122 n (%)	mRNA-1345 N=8760 n (%)	Placebo N=8757 n (%)	mRNA-1345 N=2930 n (%)	Placebo N=2916 n (%)	mRNA-1345 N=372 n (%)	Placebo N=389 n (%)
Total AEs	3106 (50.2)	2996 (48.9)	4794 (54.7)	4628 (52.8)	1706 (58.2)	1678 (57.5)	197 (53.0)	208 (53.5)
Serious AEs – Total	287 (4.6)	286 (4.7)	534 (6.1)	535 (6.1)	261 (8.9)	228 (7.8)	32 (8.6)	43 (11.1)
- Fatal	12 (0.2)	22 (0.4)	37 (0.4)	32 (0.4)	28 (1.0)	20 (0.7)	7 (1.9)	9 (2.3)
- Hospitalisation/ prolong existing hospitalisation	256 (4.1)	255 (4.2)	468 (5.3)	476 (5.4)	222 (7.6)	207 (7.1)	27 (7.3)	36 (9.3)
- Life-threatening	8 (0.1)	13 (0.2)	29 (0.3)	42 (0.5)	22 (0.8)	19 (0.7)	2 (0.5)	4 (1.0)
-Disability/incapacity	6 (<0.1)	6 (<0.1)	10 (0.1)	8 (<0.1)	5 (0.2)	5 (0.2)	1 (0.3)	1 (0.3)
- Other (medically significant)	49 (0.8)	43 (0.7)	100 (1.1)	100 (1.1)	55 (1.9)	33 (1.1)	3 (0.8)	5 (1.3)
AE leading to drop-out	18 (0.3)	28 (0.5)	43 (0.5)	40 (0.5)	31 (1.1)	28 (1.0)	7 (1.9)	9 (2.3)
Psychiatric disorders	119 (1.9)	95 (1.6)	169 (1.9)	159 (1.8)	48 (1.6)	51 (1.7)	5 (1.3)	9 (2.3)
Nervous system disorders	287 (4.6)	315 (5.1)	407 (4.6)	406 (4.6)	151 (5.2)	156 (5.3)	20 (5.4)	16 (4.1)
Accidents and injuries[1]	322 (5.2)	302 (4.9)	503 (5.7)	507 (5.8)	206 (7.0)	195 (6.7)	18 (4.8)	26 (6.7)
Cardiac disorders	87 (1.4)	93 (1.5)	210 (2.4)	205 (2.3)	114 (3.9)	112 (3.8)	12 (3.2)	13 (3.3)
Vascular disorders	211	212	412	360	147	146	14	19

MedDRA Terms	Age 60-64		Age 65-74		Age 75-84		Age 85+	
	mRNA-1345 N=6183 n (%)	Placebo N=6122 n (%)	mRNA-1345 N=8760 n (%)	Placebo N=8757 n (%)	mRNA-1345 N=2930 n (%)	Placebo N=2916 n (%)	mRNA-1345 N=372 n (%)	Placebo N=389 n (%)
	(3.4)	(3.5)	(4.7)	(4.1)	(5.0)	(5.0)	(3.8)	(4.9)
Cerebrovascular disorders [2]	0 (0)	3 (<0.1)	0 (0)	7 (<0.1)	3 (<0.1)	2 (<0.1)	0 (0)	1 (0.3)
Infections and infestations	1993 (32.2)	1891 (30.9)	2958 (33.8)	2870 (32.8)	1052 (35.9)	1058 (36.3)	140 (37.6)	138 (35.5)
Anticholinergic syndrome	NA	NA	NA	NA	NA	NA	NA	NA
Quality of life decreased	NA	NA	NA	NA	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	NA	NA	NA	NA	NA	NA	NA	NA
<other AE appearing more frequently in older patients>	NA	NA	NA	NA	NA	NA	NA	NA

1, SOC of Injury, poisoning and procedural complications

2, Central Nervous System Vascular Disorders Narrow SMQ

Comorbidities

Solicited local ARs were reported for 59.6% of participants with at least one comorbidity, compared to 57.8% of participants with no comorbidities. Similarly, solicited systemic ARs were reported for 50.2% of participants with comorbidities, compared to 46.2% of participants without comorbidities.

Incidence of unsolicited TEAEs up to 28 days and up to data cutoff was higher among participants with at least one comorbidity of interest than among those with no comorbidities of interest (23.0% vs 19.5%). Up to 28 days after injection, participants with no comorbidities experienced serious TEAEs at a rate of 0.5% in both groups. For participants with one or more comorbidities, the incidence of serious TEAEs was slightly higher with 1.0% for placebo and 0.9% for mRNA-1345. Up to the data cut-off, SAEs (9.6% vs. 4.6%) and MAAEs (45.3% vs. 36.6%) occurred more frequently in participants with comorbidities which is, however, not reflected in the frequency of related SAEs or related MAAEs. The frequency of AEs leading to study discontinuation and AESIs were comparable in both subpopulations. The results in the placebo-arm were comparable to those in the mRNA-1345 arm.

Frailty

Solicited local ARs were reported for 55.1% of participants with vulnerable/frail frailty status compared to 59.7% of participants with fit frailty status. Similarly, solicited systemic ARs were reported for 50.4% and 46.6% of participants with vulnerable/frail and fit frailty statuses, respectively.

Up to 28 after vaccination the incidence of unsolicited AEs (fit: 20.1%; Vulnerable/Frail: 22.8%) including related unsolicited AEs (5.5% and 7.1%) increased with increasing frailty status. The

incidence of SAEs up to the cutoff was higher for participants with a vulnerable/frail status (9.5%) than for participants with a fit status (5.2%). Very few related SAEs with 0 to < 0.1% of participants in the different frailty groups were reported in both mRNA-1345 and the placebo arm.

Sex

In the mRNA-1345 group, solicited ARs were reported more frequently by female participants (73.0%) than male participants (63.5%).

Within 28 days of vaccination, females reported more unsolicited TEAEs (23.0% mRNA-1345 group vs. 20.1% placebo group) compared to males (18.2% mRNA-1345 vs. 17.4% placebo). In the first 28 days, the occurrence of SAEs in the mRNA-group was 0.6% for both males and females, rising to 6.6% in males vs. 5.6% in females until the data cutoff.

Use in Pregnancy and children

Children and pregnant women are not part of this application as they do not fall within the proposed indication. However, studies are planned for these populations.

2.6.8.7. Immunological events

Not applicable

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not available

2.6.8.9. Discontinuation due to adverse events

Study P301

In the first 28 days post injection, fewer than 0.1% in both groups discontinued due to TEAEs, which increased to 0.5% in the mRNA-1345 group and 0.6% in the placebo group by the data cutoff. Most of these discontinuations were due to fatal events. Up to 28 days, TEAEs that led to study discontinuation were reported for 2 participants in the mRNA-1345 group versus 11 participants in the placebo group. One participant discontinued due to experiencing a solicited AR of fatigue with onset on Day 1 that resolved on Day 10.

Study P101

The rate of discontinuations due to adverse events was low.

2.6.8.10. Post marketing experience

Not applicable

2.6.9. Discussion on clinical safety

The safety profile of mRNA-1345 is mainly based on data from the pivotal study P301, which is a randomised, observer blinded, placebo controlled, phase 2/3 trial conducted in the target population of older adults aged ≥ 60 years. The safety data are further supported by the phase 1 study P101.

Reactogenicity as determined by solicited local and systemic ARs were collected for 7 days, while unsolicited AEs were followed for 28 days. In both studies SAEs, AESIs, MAAEs and TEAEs leading to discontinuation were followed up until EOS or up to the data lock point.

Exposure

In total 18292 participants were exposed to 50 µg of the investigational vaccine mRNA-1345 (study P301: 18184 subjects and study P101: 47 subjects), of which 1438 participants were ≥80 years in

study P301. In the P101 study participants were also exposed to different dose levels ranging from 12.5 µg to 200 µg. A small subset of participants received booster injections with up to 3 injections of mRNA-1345 overall. The safety database, with over 18000 participants, is considered of sufficient size to describe common and uncommon adverse events. Additionally, more than 17000 participants were followed up for at least 6 months.

The applicant submitted updated safety data with the most recent data cutoff of 30APR2023 in response to the D120 List of Questions.

Based on the listings of unsolicited AEs up to the data cutoff, there are 100 AEs which were considered related to the study procedure but not the investigational product whereof 52 AEs were reported in the mRNA-1345 and 48 in the placebo arm. According to the study protocol for P301, the causality of AEs to the investigational product was to be assessed by the investigator, however the relationship to the study procedure was not mentioned in the protocol and no definition for relatedness was given. The applicant provided the definition for relatedness to the study procedure upon request, which is analogous to the definition for relatedness to the investigational product. Investigators were advised to assess the relatedness of AEs to the study procedure in the CRF completion guidelines.

The majority of AEs considered related to the study procedure only occurred within 7 days after vaccination (68 AEs out of 103 AEs). Up to the most recent data cut-off, a total of 20 unsolicited AEs with solicited AR terms (fatigue, myalgia, chills, pyrexia, etc.) were assessed as related to the study procedure, whereof 6 events occurred within 7 days (3 events each in the vaccine and placebo arm). Only one event reported within 7 days in the vaccine arm ("left arm pain and myalgia") was assessed as related to the study procedure only. Thus, the applicant concluded that no change in frequency for solicited ADRs is necessary, which is endorsed.

Up to 7 days after vaccination, in total 33 AEs considered related to the study procedure only in the mRNA-1345 and 28 AEs in the placebo arm were judged as likely consistent with study procedure related events by the applicant. The majority of these events were hypertension/blood pressure increased (19 AEs in the mRNA-1345 vs. 15 AEs in the placebo arm), injection/puncture site reactions (5 vs. 5 AEs) and immunisation stress-related response including anxiety (2 vs. 4 AEs). The applicant's conclusion that these AEs are sufficiently covered in section 4.4 and 4.8 of the SmPC is endorsed and no updates of the SmPC regarding these AEs are considered warranted.

The applicant also queried investigators about AEs with dubious causality (e.g., cataract surgery, lice), long latency (e.g., sinusitis), or known pathogens (e.g., Covid-19). Although investigators often provided rationale or updated causality assessments, some events remained linked to the study procedure, primarily due to their temporal proximity to the study interventions.

The demographics were balanced between placebo group and mRNA-1345 group and are representative of the target population. Data on children and pregnant women were not included in this application, but further studies are planned for these populations. The number of discontinuations due to adverse events in both studies was very low, indicating a generally favourable tolerance among participants.

The demographic characteristics were generally balanced between the treatment arms in study P301. The median age in both study arms was 67.0 years whereof 16.0% of participants in the mRNA-1345 arm and 16.1% in the placebo arm were in the age group ≥75 years. In total, 7.9% of participants in the mRNA-1345 and 8.0% in the placebo arm were ≥80 years of age, falling short of the predefined enrolment target of 10%. LRTD risk factors were present in 7.1% of participants in the mRNA-1345 and 7.2% in the placebo arm.

Solicited Adverse Events

In study P301, reactogenicity was evaluated in 36276 participants (18174 in placebo group and 18102 mRNA-1345 group). As expected reactogenicity was higher in the verum group with 68.1% of participant reporting solicited ARs in the first 7 days compared to 38.5% in the Placebo group.

Overall, the reactogenicity profile is acceptable. The vast majority of solicited ARs were mild to moderate in intensity, with a low incidence of Grade 3 or 4 ARs. Injection-site pain was the most frequently reported solicited AR (reported by 55.9 % of participants in the mRNA-1345 group vs 13.8% in the placebo group), followed by fatigue (30.8% of participants in the mRNA-1345 group vs 20.0% in the placebo group), headache (26.7% of participants in the mRNA-1345 group vs 18.8% in the placebo group) and myalgia (25.6% of participants in the mRNA-1345 group vs 14.4% in the placebo group).

Upon request "Axillary (underarm) swelling" was replaced by "Lymphadenopathy" in section 4.8 of the SmPC. The median duration of solicited local and systemic ARs was short and was 2 days in both groups. Notably, there were several cases of reactogenicity reactions with long duration (more than 60 days). The applicant addressed this issue in the D120 response showing that the incidence and duration of solicited reactogenicity events with a duration of ≥60 days were similar between the two treatment groups. Given the large sample size, these events were reported infrequently. Most of the participants who reported these ARs had multiple comorbidities, except two. Overall, based on the provided data no causal relation with the study vaccine is concluded.

Female participants in the mRNA-1345 group reported a higher incidence of solicited ARs and unsolicited TEAEs compared to males, but the incidence of SAEs was comparable between both groups.

In study P101, observations regarding solicited ARs were consistent with study P301 with the vast majority of ARs being mild to moderate in intensity and comparable duration. Across different dose strengths in the age group 65 to 79 years (12.5 – 200 µg), solicited systemic AEs occurred in general more frequently with increasing dose strength (50.5% to 78.7%).

Unsolicited Adverse Events

The incidence of TEAEs within 28 days after injection (20.5% in the mRNA-1345 arm vs. 18.8% in the placebo arm, whereof 5.7% vs. 4.4% were related to the study injection) was affected by the persistence of solicited ARs beyond Day 7 (6.7% of subjects in the mRNA-1345 and 5.1% in the placebo arm) and occurrence of other events associated with reactogenicity. The incidence of TEAEs with onset 8 days after injection up to 28 days after injection was balanced between the groups.

TEAEs with severity ≥Grade 3 were reported by 0.7% of participants in both treatment arms and no meaningful imbalances were observed for individual PTs of this Grade.

The same trend was observed for the incidence of related unsolicited AEs, with 5.7% of participants in the mRNA-1345 group experiencing an event, compared to 4.4% in the placebo group. This disparity was primarily attributable to reactogenicity.

Upon request the applicant provided an overall overview of the duration of unsolicited AEs based on the most recent data cutoff. Overall, there were no major differences in the duration of unsolicited AEs between the mRNA1345 and placebo arm except for AESIs occurring within 28 days after vaccination (median duration: 43 days in the mRNA-1345 arm vs. 11.5 days in the placebo arm) and up to data cutoff (30 vs. 11 days).

The applicant provided a tabulation of all unsolicited AEs (i.e. unsolicited AEs, SAEs, MAAEs, AESIs and AEs leading to discontinuation) reported from study start to the data cut-off upon request. No major

imbalances on SOC level were evident except for the SOC "General disorders and administration site conditions" (6.1% in the mRNA134 vs. 5.0% in the placebo arm) which was mainly due to reactogenicity-related AEs, e.g. fatigue (2.8% vs. 2.4%), injection site pain (0.7% vs. 0.3%), Injection site lymphadenopathy (0.4% vs. 0.1%) and injection site erythema (0.3% vs. <0.1%). Also, treatment-related TEAEs were more frequent in the mRNA-1345 group, mainly due to reactogenicity-related events and nervous system disorders like headaches.

Furthermore, the applicant reviewed the numerical imbalances in events of pneumonitis, respiratory syndrome, seborrheic dermatitis, trigger finger and syncope. Although there was a numerical imbalance between the study arms, no new safety concerns were identified from the presented data. It is considered that monitoring through routine pharmacovigilance is sufficient.

The applicant discussed in the D120 response PTs with two or more related TEAEs in the mRNA-1345 arm within 28 days and numerical imbalances between the two arms. These PTs included dizziness, rash, back pain, peripheral swelling, hypertension and injection site pruritus. Based on this discussion the applicant concluded that no update of the SmPC regarding these PTs is warranted. However up to 7 days after vaccination, there was a numerical imbalance in events of dizziness between the mRNA-1345 (13 events) and the placebo arm (8 events) whereof 6 events vs. 1 event were considered related to the study vaccination. Up to 28 days, there were reported 27 events of dizziness in the mRNA-1345 arm whereof 7 cases were considered related vs. 23 events (1 related case) in the placebo arm. The applicant included "dizziness" as an ADR and listed dizziness under the SOC "Nervous system disorders" with a frequency "Uncommon" on request by the Rapporteurs.

Furthermore, 4 participants in the mRNA-1345 arm and 1 participant in the placebo arm, had events of injection site pruritus assessed by the investigator as related to the mRNA-1345 vaccine and 4 of the 5 events in the mRNA-1345 arm occurred concurrently with injection site pain. Injection site pruritus is a well-known but uncommon adverse reaction to vaccines in general and is listed as an ADR in the product information for several vaccines and in particular mRNA-vaccines. The applicant included "Injection site pruritus" as an ADR in Section 4.8 of the SmPC under the SOC "General disorders and administration site conditions" with a frequency of "Rare" as requested by the Rapporteurs.

In Study P101, TEAEs were overall balanced between the mRNA-1345 groups and the placebo groups, however the group sizes in study P101 are small and no clear trend regarding a possible dose effect on the frequency of unsolicited and related AEs were detectable.

The applicant was asked to provide an assessment comparing the severity of confirmed RSV cases in placebo and mRNA-1345 vaccinated subjects. In the mRNA1345 arm, a lower percentage of participants with confirmed RSV-LRTD with ≥2 Symptoms presented shortness of breath as symptom compared to the placebo arm (11 out of 47 (23.4%) vs. 43 out of 127 (33,8%). In addition, no meaningful differences in other parameters of RSV infection indicative of more severe disease were evident. Taken together, there are no apparent differences in the disease severity in participant with confirmed RSV-infection between the mRNA-arm and the placebo arm. Thus, there is no indication of a risk of vaccine-associated disease enhancement after mRNA-1345 vaccination.

Medically attended adverse events

In study P301, MAAEs excluding Per-protocol Illness Visits, were reported more frequently in the mRNA-1345 group (8.8%) than in the placebo arm (8.4%) up to 28 days after injection and up to data cut-off (39.2% vs. 38.1%). In P101, MAAEs including excluding Per-protocol Illness Visits, were reported by 59.6% vs 35.6% for adults aged 65-79 years. Related MAAEs excluding Per-protocol Illness Visits up to 28 days post-injection were slightly higher in the mRNA group of study P301 with 66 participants (0.4%) reporting 90 events, compared to 51 participants (0.3%) in the placebo group

reporting 57 events. MAAEs varied across repeated doses and dose groups in Study P101. There are no safety concerns regarding MAAEs.

Adverse events of special interest and SMQs

In study 301 and study P101, thrombocytopenia, new onset of or worsening of specific neurologic diseases (Bell's palsy/facial paralysis, GBS, ADEM, and seizures), anaphylaxis, and myocarditis/pericarditis were collected as AESI until EOS/data lock point. Overall, AESIs were very infrequent and occurred at a similar rate in both treatment groups (<0.1% in each arm) up to the most recent data cutoff. Only a few AESIs, i.e. facial paralysis, seizure and platelet count decreased were considered to be related in the mRNA-1345 group.

Upon request the applicant provided data on the duration of AESIs down to PT level and discussed imbalances in duration of the AESIs. The applicant explained the observed imbalances between the study arms with a combination of multiple factors such as the low incidence of AESIs, multiple disparate medical conditions with expected different durations (e.g., seizures vs. chronic conditions) incorporated in AESIs, ongoing events as per data cutoff (30. April 2023) and events with missing end dates. Considering the low number of AESIs reported up to the data cutoff (39 in the mRNA-1345 vs. 37 in the placebo arm) the applicant's explanation is considered reasonable. On PT level, events of facial paralysis and Bell's palsy lasted longer in the mRNA-1345 arm than in the placebo group (median duration of facial paralysis: 114 vs. 2.5 days and of Bell's palsy: 52 vs. 8 days). The applicant proposed including Peripheral facial nerve paralysis (e.g., Bell's palsy) as ADR in 4.8 of the SmPC including a footnote specifying the cases reported in clinical studies with mRNA-1345, which was endorsed.

Up to 7 days postinjection, there were no reported cases of myocarditis or pericarditis and furthermore, no such AESIs were observed in the mRNA-1345 group within 28 days after the injection. In the mRNA-1345 arm there where 2 CEAC-adjudicated cases of acute pericarditis reporting 3 events with a time to onset (TTO) >42 days after study injection, and 1 case of myocarditis, versus 1 case of pericarditis in the placebo arm. None of these cases were evaluated to be related.

Urticarial events were more frequently reported in the mRNA-1345 group. The applicant was asked to analyse the urticaria cases (in particular delayed or chronic urticaria), assess causality and propose any needed updates to the SmPC/PIL. The majority of the urticaria events in the mRNA-1345 arm (44 out of 48 cases) had an onset later than day 7 and, thus, were categorised as delayed onset urticaria. Of a total 6 related events of urticaria in the mRNA-1345 arm, 3 events were delayed urticaria (onset day 9, 12 and 17) and 2 events were chronic urticaria. In the placebo arm no event of delayed or chronic urticaria was considered related.

For chronic urticaria the applicant has only presented the number of events up to the data cutoff in the response and stated that there was no imbalance between the study arms. No assessment regarding the most relevant timepoint up to day 28 after vaccination has been presented by the applicant. From the applicant's listing for each participant from study P301 (listing 16.2.7) 4 events of chronic urticaria with a TTO within 28 days (day 1, 12, 15 and 20) compared to 1 event in the placebo arm (TTO D27) was identified. In total two related events of chronic urticaria in the mRNA-1345 arm were reported versus 0 in the placebo arm. At D120 there were several discrepancies regarding the numbers of urticaria events in the applicant's response. The applicant explained the discrepancies in the number of urticaria cases/events provided in the D120 AR response and provided a new table with number of participants and reported events, which resolved this issue.

The applicant was requested to update the SmPC to reflect that urticaria as adverse reaction to mResvia can occur as delayed onset urticaria. The applicant proposed to list urticaria as an example for

the ADR "Hypersensitivity (e.g. urticaria, etc)" in section 4.8 of the SmPC with the frequency uncommon. However, several cases of urticaria have been reported including cases considered related to the investigational product. Urticaria was included as a stand-alone ADR in the SOC "Skin and subcutaneous tissue disorders" with a frequency "rare" on request by the Rapporteurs. A footnote specifying that urticaria can manifest with delayed onset or as chronic urticaria was included.

The applicant discussed the imbalances in the narrow/broad SMQ for GBS between the study arms upon request, in particular the related cases of facial paralysis, hypoaesthesia and paraesthesia in the mRNA-1345 arm. No events of GBS or ADEM were reported up to data cutoff and no safety concerns were identified regarding facial paralysis.

The applicant discussed on request why two events of Hypoesthesia in the mRNA-1345 arm were considered related to the study procedure but not to the mRNA-1345 vaccine. The applicant provided the narratives for the two events. One event of "face numbness" occurred concurrently with events of "face tightness" and post-vaccine anxiety at day one and one event of "right upper extremity numbness" at day 61 was attributed to "blood draws". Considering the information provided in this discussion no updates regarding hypoesthesia in the SmPC were needed.

Up to the data cut-off, in total 10 participants (10 events) in the mRNA-1345 group and 4 participants (4 events) in the placebo arm reported postmenopausal bleeding related events (vaginal haemorrhage, postmenopausal haemorrhage, intermenstrual bleeding and abnormal uterine bleeding), whereof none were evaluated to be related by the investigator. TTO were reported as ≤ 28 days for 2 participants in the mRNA-1345 group vs. 1 participant I the placebo arm. PTs reported by more than 2 participants were vaginal haemorrhage in 4 participants (4 events) in mRNA-1345 group vs. 1 participant in the placebo arm and Postmenopausal haemorrhage in 3 versus 1 participant. There was one serious AE (PT Post Menopausal Bleeding) reported in the mRNA-1345 group vs 0 in the placebo arm. The applicant will include postmenopausal bleeding as a safety topic in PSURs.

Within the narrow/broad SMQ for angioedema there is an imbalance in events between the mRNA-1345 and the placebo arm both up to 7 days and 28 days post vaccination. Similarly, an imbalance in reported events within the SMQ Hypersensitivity between the mRNA and the placebo arm was evident up to 7, 28 days post vaccination and up to the data cutoff.

Within the SMQ angioedema 6 events reporting PTs that can indicate a hypersensitivity reaction, for instance, hypersensitivity, wheezing and swelling were considered related to the mRNA-1345 vaccine compared to 0 to the placebo up to 7 days post vaccination. In addition, events within the narrow SMQ hypersensitivity considered related in the mRNA-1345 arm included rash including erythematous rash and exfoliative rash (6 participants), and dermatitis, hypersensitivity non-urticarial dermatitis, erythema, pruritus and wheezing (1 participant each).

It is well-established that hypersensitivity or allergic (anaphylactic) reaction can be triggered by vaccines and a general warning regarding these undesirable effects of vaccines is already included in 4.4. of the SmPC for mResvia. Considering the imbalances identified overall in the SMQ for angioedema and the SMQ hypersensitivity as well as in related events of different PTs within these SMQs and with relevant TTO, there is considered to be a reasonable possibility for a causal association between hypersensitivity and the mRNA-1345 vaccine. Hypersensitivity has been listed in the SOC "immune system disorders" as requested.

Serious Adverse Events and Death

In study P301, the number of participants experiencing SAEs was similar in the mRNA-1345 group (115 (0.6%)) compared to the placebo group (111 (0.6%)) in the first 28 days (6.1% and 6.0% in the mRNA-1345 group and placebo group, respectively, up to data cutoff). The mRNA-1345 group had a

higher incidence of events in the SOC infections and infestations with 26 (0.1%) incidents in the mRNA-1345 group and 10 (<0.1%) in the placebo group (1.3% vs. 1.4% until data cut-off).

In the SOC cardiac disorders, the placebo group had a marginally higher number of reported events, 17 (<0.1%) compared to the mRNA-1345 group, 14 (<0.1%). In the SOC metabolism and nutrition disorders, a slightly higher incidence of SAEs was noted in the mRNA-1345 group, 8 (<0.1%), compared to the placebo group, 2 (<0.1%).

The occurrence of SAEs related to mRNA 1345 was very low, with <0.1% (four participants in mRNA-1345 group and five participants in the placebo group) of participants experiencing an event deemed related until data cutoff. Considering that each SAE judged as related to the vaccine was reported only by one participant, it is not possible to draw definitive conclusions.

Over the course of study P101 and P301, 25 participants (0.1%) in the mRNA-1345 group and 24 participants (0.1%) in the Placebo group experienced a fatal AE. Overall, a balanced incidence of fatal events between the mRNA-1345 and placebo groups was seen, with investigators judging none of the fatal events related to the vaccination.

AEs leading to study discontinuation

In study P301, 99 participants (0.5%) in the mRNA-1345 and 105 participants (0.6%) in the placebo arm discontinued the study due to experiencing an AE up to the database lock date, whereof 2 in the mRNA-1345 and 11 participants in the placebo group discontinued the study within 28 days after vaccination. A total of 81 AEs leading to study discontinuation in the mRNA-1345 arm and 82AEs in the placebo arm were due to deaths; all of them were considered not related to the study vaccinations. Only one AE leading to study discontinuation was considered related to the study vaccination: a case of Grade 1 fatigue with onset 1 day after vaccination with mRNA-1345, which resolved after 10 days.

In study P101, no AEs leading to study discontinuation occurred in the 50-µg mRNA-1345, placebo or any other group. One participant in the 12.5 µg mRNA-1345 group discontinued study vaccination (booster vaccination) due to a SAE of gunshot wound. Three other participants had consent withdrawal as the primary reason for study discontinuation, but it is noted that consent was withdrawn due to experiencing AEs including hypertension (TTO D33), postvaccination symptoms (headache, fatigue, myalgia, and arthralgia), and arthritis and personal issues. The participants that withdrew from study P101 due to an AE had all received a higher dose than 50 µg.

Clinical laboratory testing

Overall, there was a higher incidence of TEAEs reported for PTs associated with laboratory tests in the mRNA-1345 groups than placebo group (SOC investigations: 14 (5.9%) vs. 0 participants). These TEAEs were reported in a single participant each with the exception of activated partial thromboplastin time (aPTT) prolonged which was reported by one participant in the 12.5 µg group and one in the 200 µg group, both evaluated to be related by investigator. In addition, one case of prothrombin time (PT) prolonged was reported after the first vaccination in the 50 µg group and evaluated to be related by investigator.

In the age cohort 18-49 one participant in the single injection 100 µg mRNA-1345 group had a TEAE of aPTT prolonged lasting from Day 10 to Day 29 and one participant in the 3-injection 100 µg mRNA-1345 group had a MAAE of WBC count increased from Day 6 to Day 24 (after Dose 3) and a TEAE of aPTT prolonged from Day 29 to Day 46 (after Dose 3). All of these laboratory events were mild, nonserious, and unrelated to study vaccine per investigator. One participant of Japanese descent had a Grade 4 high prothrombin time on Day 29 which as evaluated as not related by investigator.

The applicant was requested to discuss the imbalance in TEAEs related to prothrombin function, i.e. high PT and aPTT and PT prolonged in study P101 as well as any imbalances in other coagulation

related PTs in study P101 and P301. In study P301, a single case of "prolonged bleeding time" was reported in the mRNA-1345 group, with no similar events in the placebo group. At the cutoff, 5 participants in the mRNA-1345 group experienced coagulation-related TEAEs versus 4 in the placebo group, with most events being mild to moderate in intensity but including two severe cases that were reported in the mRNA-1345.

Study P101 reported 7 coagulation-related AEs across both older and younger adult cohorts without a specific pattern in treatment arm or onset time. In total, two related events of coagulation PTs were reported following administration of 50 µg mRNA-1345 in study P301 and P101. Based on the safety data, there was insufficient evidence to establish causality for coagulation-related AEs and no new safety concern was identified.

2.6.10. Conclusions on the clinical safety

Based on the evidence available, one dose of mRNA-1345 demonstrates an acceptable safety profile, characterised by transient and predominantly mild to moderate reactogenicity, in the studied population of older adults. The most frequently reported reactogenic AEs by PT were injection-site pain, fatigue, headache, myalgia and arthralgia and reactogenicity decreased with increasing age, as expected. Most unsolicited AEs were of mild to moderate severity and the numbers of SAEs and deaths were comparable to the placebo group. No causal relationship was established between the vaccine and the fatal cases.

No new safety issues have been identified based on the submitted safety data.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 35: Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

2.7.2.1. Routine pharmacovigilance activities

The routine pharmacovigilance activities are as follows:

- Specific adverse reaction follow-up questionnaire for myocarditis/pericarditis:
- A targeted follow-up questionnaire to collect structured clinical details of myocarditis or pericarditis will be used for any cases of myocarditis or pericarditis that are reported during the post-marketing period.

2.7.2.2. Summary of additional PhV activities

Table 36: 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-P101 A Phase 1, Randomized, Observer-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting respiratory syncytial virus (RSV), in Healthy Younger Adults Aged 18 to 49 Years, Women of Child-Bearing Potential Aged 18 to 40 Years, Healthy Older Adults Aged 65 to 79 Years, Japanese Older Adults Aged ≥60 Years, and RSV-Seropositive Children Aged 12 to 59 Months Ongoing	**Primary Objectives:** • To evaluate the tolerability and reactogenicity of a single injection of up to 5 dose levels of mRNA-1345 in younger adults, women of child-bearing potential, and older adults, including Japanese older adults. • To evaluate the tolerability and reactogenicity of 3 injections of the middle dose level of mRNA-1345 given 56 days apart in younger adults. • To evaluate the tolerability and reactogenicity of a booster injection of mRNA-1345 given approximately 12 months after the primary injection in older adults. • To evaluate the tolerability and reactogenicity of 3 injections of 2 dose levels of mRNA-1345 given 56 days apart in RSV-seropositive children.	• Myocarditis/ pericarditis • Long term safety	Study initiation: Study completion: Final study report (paediatrics): Final study report (other populations):	30 Sep 2020 Aug 2024 Feb 2025 Jul 2025

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
mRNA-1345-P301 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age Ongoing	**Primary Objectives:** • To evaluate the safety and tolerability of the 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.	• Myocarditis/ pericarditis • Long-term safety	Study initiation: Study completion: Final study report:	17 Nov 2021 30 Sep 2025 Jul 2026
mRNA-1345-P302 A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Co-administered 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 co-administered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of co-administered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of co-administered RSV vaccine on the immune response to influenza. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345 co-administered with mRNA-1273.214. • To evaluate the effect of co-administered mRNA-1273.214 on the immune response to RSV-A. • To evaluate the effect of co-administered RSV vaccine on the immune response to SARS-CoV-2. **Primary Objectives (Part C):** • To evaluate the safety and tolerability of a booster dose of mRNA-1345 administered at Year 1 following a primary dose. • To evaluate immune response to RSV-A of a booster dose of mRNA-1345 administered at Year	• Myocarditis/ pericarditis • Co-administration with other vaccines • 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 Dec 2024 Nov 2025

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	1 following a primary dose. • To evaluate the safety and tolerability of booster dose of mRNA-1345 administered at Year 2 following a primary dose. • To evaluate immune response to RSV-A of a booster dose of mRNA-1345 administered at Year 2 following a primary dose.			
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 RSV-A nAb response to a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥ 18 to <60 years) compared with that in high-risk older adults (≥ 60 years). **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSV-B nAb responses to 2 doses of 50 µg mRNA-1345 injection administered 57 days apart in immunocompromised participants ≥18 years of age.	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Long term safety	Study initiation: Study completion: Final Study report	06 Oct 2023 31 Mar 2026 Feb 2027
mRNA-1345-P902 Post-Authorisation 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 Planned	**Primary Objectives:** 1) Describe the uptake of the mRNA-1345 vaccine and characterise mRNA-1345 vaccine recipients 2) Estimate incidence of pre-defined Safety Topics of Interest among mRNA-1345 vaccine recipients 3) For signal detection, compare the observed incidence rates of pre-defined Safety Topics of Interest among mRNA-1345 vaccine recipients with expected incidence rates of pre-defined Safety Topics of Interest from a similar comparator cohort(s) 4) When a safety signal is detected based on pre-defined statistical threshold, • Compare incidence rates of pre-defined Safety Topics of Interest in the risk interval with incidence rates in the post-vaccination control	• Myocarditis/ pericarditis • Co-administration with other vaccines • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Apr 2024[1] Jul 2027[1, 2]

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	interval in a self-controlled risk interval analysis. Or • Compare the observed incidence rates of pre-defined Safety Topics of Interest among mRNA-1345 vaccine recipients with incidence rates of pre-defined Safety Topics of Interest in a similar matched cohort who did not receive the mRNA-1345 vaccine **Secondary Objectives:** Secondary objectives are identical to the primary, but focused on specific populations considered to have missing information, including but not limited to • Immunocompromised patients • Stratification by age group and sex • Patients who, at cohort entry, had recently received other selected vaccines to prevent diseases other than the mRNA-1345 vaccine • Patients with autoimmune or inflammatory disorders			
mRNA-1345-P903 Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe Planned	**Primary Objectives:** 1) Describe the uptake of the mRNA-1345 vaccine and characterise mRNA-1345 vaccine recipients 2) Estimate incidence of pre-defined adverse events of Safety Topics of Interest among mRNA-1345 vaccine recipients 3) For signal detection, compare the observed incidence rates of pre-defined Safety Topics of Interest among mRNA-1345 vaccine recipients with expected incidence rates of pre-defined Safety Topics of Interest from a similar comparator cohort(s) 4) When a safety signal is detected based on pre-defined statistical threshold, • Compare incidence rates of pre-defined Safety Topics of Interest in the risk interval with incidence rates in the post-vaccination control	• Myocarditis/ pericarditis • Co-administration with other vaccines • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Oct 2024[3] May 2028[2, 3]

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	interval in a self-controlled risk interval analysis. Or • Compare the observed incidence rates of pre-defined Safety Topics of Interest among mRNA-1345 vaccine recipients with incidence rates of pre-defined Safety Topics of Interest in a similar matched cohort who did not receive the mRNA-1345 vaccine **Secondary Objectives:** Secondary objectives are identical to the primary but focused on specific populations considered to have missing information, including but not limited to • Immunocompromised patients • Stratification by age group and sex • Patients who, at cohort entry, had recently received other selected vaccines to prevent diseases other than the mRNA-1345 vaccine • Patients with autoimmune or inflammatory disorders • Stratification by country where appropriate			

[1] The proposed timeline is subject to change depending on the US BLA approval date and real-world database selection.

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

[3] The proposed timeline is subject to change depending on the MAA approval date and real-world database selection.

The pharmacovigilance plan includes the continuation of phase 1-3 studies as well as two post-authorisation safety studies (PASS), one to be conducted in the US and the second to be conducted in the EU. The two PASS will use administrative healthcare databases to characterise the risk of predefined adverse events of special interest (AESIs) in the older population and within subgroups defined by age, sex, immunocompromised status, coadministration of other vaccine(s), and status of autoimmune or inflammatory disorders. The study synopses of both PASS are proposed in Annex 3 of the RMP.

The fundamental research question of this study: Is the risk of each pre-defined Safety Topics of Interest among persons vaccinated with mRNA-1345 higher than the expected risk in a similar population in the absence of mRNA-1345?

The list of Safety Topics of Interest currently includes

Primary Safety Topics of Interest:

- Myocarditis
- Pericarditis

Secondary Safety Topics of Interest:

- Acute disseminated encephalomyelitis (ADEM)
- Acute myocardial infarction (AMI)
- Anaphylaxis
- Atrial fibrillation
- Bell's palsy
- Guillain-Barré syndrome (GBS)
- Venous thromboembolism (VTE)
- Non-haemorrhagic stroke (NHS)
- Non-haemorrhagic stroke / Transient ischemic attack (TIA)

Background rates of Safety Topics of Interest among at least one historical cohort in the post COVID-19 era, who are similar to mRNA-1345 vaccinees, will be estimated. For most acute Safety Topics of Interest, self-controlled risk interval analysis will be conducted. Contemporaneous cohort(s) similar to mRNA-1345 recipients will be considered when the assumptions required for executing the self-control risk interval design cannot be met and the ascertainment of vaccination in the target population is reasonably complete.

Secondary objectives will focus on specific populations, including but not limited to

- Immunocompromised patients
- Stratification by age group and sex
- Patients who, at cohort entry, had recently received other selected vaccines to prevent diseases other than the mRNA-1345 vaccine (e.g., COVID-19 and influenza vaccines)
- Patients with autoimmune or inflammatory disorders
- By country when appropriate

Overall, the pharmacovigilance plan covers all important safety concerns previously identified. The protocols of both PASS will be submitted to the PRAC for assessment and approval when available. The Safety topics of Interest will be discussed, and more particularly, the inclusion of Idiopathic/Immune thrombocytopenia, Seizures and Transverse myelitis should be considered.

2.7.2.3. Overall conclusions on the PhV Plan

The Committee, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The Committee also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

2.7.3.1. Routine Risk Minimisation Measure

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

2.7.3.1. Summary of additional risk minimisation measures

There are no additional risk minimisation measures

2.7.3.2. Overall conclusions on risk minimisation measures

The Committee having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7.4. Conclusion on the RMP

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

Not applicable.

2.9.3. Quick Response (QR) code

Not applicable.

The company did not meet the requirements for the use of mobile scanning and other technologies during the marketing authorisation procedure. Thus, the company is recommended to submit the request via an 'Article 61(3) Notification post-approval' (REC). The company commits to the declaration form related to the use of mobile scanning and other technologies together with requested information after marketing authorisation, by December 2024.

Area	Description	Due Date
Labelling	The applicant commits to submit the request for the use of mobile scanning and other technologies and provide the declaration form via an Article 61(3) Notification post-approval (REC).	December 2024

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, mResvia (Single-stranded 5' capped mRNA encoding the Respiratory syncytial virus glycoprotein F stabilised in the prefusion conformation) is included in the additional monitoring list as new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed therapeutic indication changed from:

RSV mRNA vaccine is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) and acute respiratory disease (ARD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older. (initial indication at submission of MAA)

To:

mRESVIA is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in adults 60 years of age and older. (current agreed indication statement SmPC section 4.1 after D180 responses)

Respiratory syncytial virus (RSV) is a ribonucleic acid (RNA) virus belonging to the genus Orthopneumovirus within the family Pneumoviridae of which 2 antigenically distinct subtypes exist, RSV-A and RSV-B.

RSV has been identified as one of the important aetiologies of acute respiratory infection (ARI) in older adults and is increasingly recognised as a major cause of illness in all high-risk adults, including those with chronic lung and heart disease (Falsey et al 2005, Shi et al 2020). The overwhelming majority of RSV mortality in industrialised countries occurs in those that are above 65 years of age (Korsten et al 2021). RSV is transmitted primarily via aerosolised droplets from the sneeze, cough, or breath of an infected person, or via contamination of environmental surfaces with infectious secretions. Upper respiratory symptoms typically begin within several days of RSV infection. The virus may descend to the lower respiratory tract, leading to wheezing, bronchiolitis and potentially hospitalisation, respiratory failure, mechanical ventilation, and even death. Infections with RSV follow a seasonal pattern, typically occurring in the Northern hemisphere between the months of November and April, and in the Southern hemisphere between March and October.

3.1.2. Available therapies and unmet medical need

Treatment

An antiviral agent, ribavirin, is licensed for the treatment of RSV infection in the United States and some EU member states. This drug is not recommended in the United States or EU guidelines.

Prevention

Currently, there are two licensed vaccines for the prevention of RSV-associated diseases in adults ≥60 YoA.

Unmet medical need

Respiratory syncytial virus (RSV) infections in the elderly population in Europe constitutes a public health concern. The mRNA-1345 vaccine candidate uses a relatively new technology within the field of vaccines, where only two mRNA vaccines are currently approved, both for the prevention of COVID-19

3.1.3. Main clinical studies

The main evidence for efficacy for RSV mRNA vaccine is based on study mRNA-1345-P301 (referred to as Study P301), an ongoing Phase 2/3 randomised, observer-blind, placebo-controlled, case-driven pivotal safety and efficacy study.

3.2. Favourable effects

Vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms, and VE of 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms was demonstrated in an interim

analysis CSR of Study P301 with a median follow-up time of 3.7 months. Additional analysis with a median follow-up time of 8.6 months resulted in VE of 63.3% (48.7, 73.7) against RSV-LRTD with ≥2 symptoms, and VE of 63.0% (37.3, 78.2) against RSV-LRTD with ≥3 symptoms.

The humoral immunogenicity results showed that the mRNA-1345 vaccine is able to induce a durable immune response in the intended target population. In addition, evidence of a robust and persistent RSV preF-specific T cell response was demonstrated through a follow up period of 3 months.

3.3. Uncertainties and limitations about favourable effects

The determination of favourable effects of the mRNA-1345 RSV vaccine is based on vaccine efficacy from a pivotal phase 2/3 Study P301 with a limited follow-up of subjects. The ongoing pivotal case-driven phase 3 clinical study in adults ≥60 years of age met the primary safety and efficacy endpoints based on prespecified interim data. This first interim analysis is considered as the primary analysis based on a protocol amendment, since the primary endpoints were met at the time of this interim analysis. Subsequent data from a later time points will be considered supplementary. Bearing in mind that the final analysis may alter the outcome of the primary efficacy objectives, further data from later timepoints are requested. In addition, it is unclear how this has affected the continuance of the study and the blinding of the participants and study staff. This is particularly important, seeing as the 24 months follow-up will provide important information on the persistence of protection and the need for further doses.

The humoral immunogenicity data from the ongoing supportive Phase 1 study are based on a limited targeted population for the sought indication (adults 65 to 79 Years). A trend of lower immune response with increasing age is observed.

Waning of immunity in terms of nAbs and binding Abs is demonstrated over time until month 12, with neutralising antibodies (GMTs) still higher than baseline. However, the immune response observed cannot be directly translated to efficacy as there is no correlate of protection. The immunogenicity data from Study P301 up to Day 29 have been provided in the applicant's D120 responses. Comparisons of immunogenicity across studies were not possible at this time. Data in high-risk immunocompromised populations are currently lacking.

The sought indication is for adults ≥60 years, however, the age group >80 years is poorly represented. In the pivotal trial, participants >80 years comprised only 5.6 %, while the targeted inclusion was 10 %. In addition, the number of participants with LRTD risk factors was relatively low with <10% of participants having LRTD risk factors. Although participants living in nursing homes were not excluded, the emphasis for inclusion was mainly on participants that were self-reliant for self-care and daily living.

For most secondary and exploratory endpoints, no data have been submitted for the pivotal Phase 2/3 trial. The applicant has been asked to provide all available data on immunogenicity for RSV-A and RSV-B at all time points according to the secondary and explorative objectives and endpoints from Study P301. This is especially important concerning the oldest age groups (>80 years) as no events have been reported in either placebo or active arm in the initial analysis, and only few events have been reported in the additional analysis, and thus no efficacy can be estimated in this subgroup.

A lower VE against RSV-B compared to RSV-A was observed in the pivotal study. This was accompanied by lower nAb titres against RSV-B as compared to RSV-A. The study was not powered to determine efficacy against the individual RSV subtypes. It cannot be excluded that lower VE and lower nAb GMTs against RSV-B are due to the use of the F-protein mRNA-sequence from RSV-A in the vaccine.

No evidence of enhanced disease was observed in the pivotal clinical trial. The target age group (>60 years) is assumed to be non-naïve which alleviates the potential for enhanced disease following RSV vaccination. Binding antibody responses (to both PreF and PostF conformations) are generated following vaccination. It is uncertain whether these may have the potential to contribute to enhanced disease in naïve individuals (albeit rare) in this age group (e.g. via formation of immune complexes).

Data on cell-mediated immune responses formed an exploratory endpoint on a separate clinical study.

No data are available relating to the persistence of protection from the pivotal phase 2/3 trial and the duration of protection is not clear. Limited data (n=47) from the phase 1 clinical trial showed that neutralising antibody were highest in the first month after vaccination and thereafter waned during the first year to levels above baseline. Since responses to RSV-B were lower than to RSV-A, the duration of protection against RSV-B may be shorter.

A single administration is selected because the target population is assumed to be non-naïve and immunisation will boost responses induced from prior infection. The dose level selected for the efficacy study was 50µg even though data from 25µg doses showed similar immunogenicity. The efficacy of the 25µg dose is not known.

3.4. Unfavourable effects

The clinical safety profile of mRNA-1345 was largely resulting from data collected in study P301. The safety of mRNA-1345 is mainly characterised by local and systemic reactions with the most common adverse reactions being injection site pain (55.9%), fatigue (30.8%), headache (26.7%), and myalgia (25.6%). Most adverse reactions occurred within 1 to 3 days following vaccination and were mild to moderate in severity. No Grade 4 local ARs were reported with only Grade 4 systemic AR being fever (0.2% in both groups). The majority of these local and systemic adverse reactions resolved within 1 to 3 days, with a median duration of 2 days. Higher incidence of ARs was reported in younger participant (60 to 69 years of age) and female participants. A higher incidence for unsolicited AEs was reported in the older age group. Urticaria was included as an ADR in the SmPC based on the higher incidence of urticaria in the mRNA-1345 group [15 participants (<0.1%) whereof 6 related events] compared to placebo arm [5 participants (<0.1%) whereof 1 related event] up to 28 days post-injection and the lack of alternate aetiologies identified. In addition, dizziness, hypersensitivity and injection site pruritus were found to have a reasonable possibility for a causal association and inclusion in 4.8 was considered warranted by the CHMP.

3.5. Uncertainties and limitations about unfavourable effects

In the clinical studies for the current MAA, the safety of mRNA-1345 has not been specifically evaluated for individuals with compromised immunity, autoimmune, or inflammatory disorders. Subjects with a history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease were excluded per study protocol for study P301, however, subjects with stable autoimmune diseases that do not require systemic immunosuppressants were permitted. A dedicated clinical trial in immunocompromised individuals is being planned.

Potential risks such as myocarditis/pericarditis remain important concerns, as these were discovered only in the widespread use of other mRNA vaccines. Pericarditis and myocarditis are listed as an important potential risk in the RMP. There were 2 cases of medically attended pericarditis and 2 cases of myocarditis in the mRNA 1345 vaccinated compared to 1 case of pericarditis in the placebo group at data cut-off, all evaluated as unrelated.

Furthermore, the available data lacks information on potential long-term safety issues and interactions with other vaccines. Interactions with other vaccines and use in immunocompromised patients will be further characterised by studies such as the ongoing mRNA-1345-P302 study and the planned mRNA-1345-P902 and mRNA-1345-P903 studies.

In the RMP use in immunocompromised and individuals with autoimmune or inflammatory disorders, interaction with other vaccines and long-term safety are included as missing information.

There are no data on the use in breast-feeding women, pregnant women and children, since they were not included in the clinical development programme to support the indication in individuals ≥60 years. However, the applicant is planning and conducting studies, which will assess the safety in this populations.

3.6. Effects Table

Table 37: Effects Table for mResvia.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
VE measured against the first occurrence of RSV-LRTD, with follow-up period 3.7 months						
VE	≥2 or more symptoms		mRNA-1345	Placebo	HR (%, 95.88% CI) 83.7 (66.0, 92.2)	Study P301
VE	≥3 or more symptoms		mRNA-1345	Placebo	HR(%,96.36% CI) 82.4 (34.8, 95.3)	Study P301
VE measured against the first occurrence of RSV-LRTD, with follow-up period 8.6 months						
VE	≥2 or more symptoms		mRNA-1345	Placebo	HR (%) 63.3 (48.7, 73.7)	Study P301
VE	≥3 or more symptoms		mRNA-1345	Placebo	HR (%) 63.0 (37.3, 78.2)	Study P301
Unfavourable Effects						
Any solicited ARs	Incidence of solicited ARs	%	68.1	38.5		Study P301
Any local solicited ARs	Incidence of solicited local ARs	%	58.3	16.2		Study P301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Any systemic solicited ARs	Incidence of solicited systemic ARs	%	47.4	32.9		Study P301
Injection site pain	Incidence of injection site pain	%	55.9	13.8		Study P301
Fatigue	Incidence of fatigue	%	30.8	20.0		Study P301
Headache	Incidence of headache	%	26.7	18.8		Study P301
Myalgia	Incidence of Myalgia	%	25.6	14.4		Study P301
Arthralgia	Incidence of Arthralgia	%	21.7	14.0		Study P301
Urticaria	Incidence of Urticaria	%	<0.1	<0.1	Imbalance identified in the angioedema and hypersensitivity SMQs	Study P301
Grade 3 or 4 Local ARs	Incidence of Grade 3 or higher Local ARs	%	3.1	1.7	Most frequent was injection site pain	Study P301
Grade 3 or 4 Systemic ARs	Incidence of Grade 3 or higher Systemic ARs	%	4.0	2.8	Most frequent was fatigue	Study P301
ARs Persisted beyond 7 days	Incidence of ARs Persisted beyond 7 days	%	6.7	5.1		Study P301
Unsolicited AEs	Incidence of AES not solicited within 28 days postinjection	%	20.5	18.8		Study P301
Severe AEs	Severe/≥Grade 3 AEs within 28 days post-vaccination	%	0.7	0.7	Most frequently reported were fatigue an arthralgia	Study P301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
SAEs	Incidence of Serious Adverse Events within 28 days	%	0.6	0.6		Study P301

Abbreviations:

HR: Hazard Ratio
ARs: Adverse Reactions
AEs: Adverse Events
SAEs: Serious Adverse Events
SMQs: Standardized MeDRA Queries

Notes:

Severe AEs: Unsolicited severe AEs are events that prevent the participant's daily activity and require intensive therapeutic intervention (unsolicited AEs); Solicited ARs were categorised according to "The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Vaccine efficacy of 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms, and VE of 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms was demonstrated in the initial interim analysis in subjects ≥60 years of age. The follow-up time for the majority of subjects was rather short (3.7 months). Therefore, more robust efficacy results from a later data cut-off were requested. In the updated analysis, >90% of participants were followed for at least 6 months following IP administration. While the data confirmed a clinically relevant VE it was considerably lower than the short-term VE observed in the primary analysis. Vaccine efficacy for the prevention of RSV-LRTD with ≥ 2 symptoms dropped from 83.7% (95% CI: 66.0%, 92.2%) to 63.3% (95% CI: 48.7%, 73.3%) and for the prevention of RSV-LRTD with ≥ 3 symptoms it dropped from 82.4 (95% CI: 34.8%, 95.3%) to 63.0% (95% CI: 37.3%, 78.2%).

As the primary endpoints were met in the interim analysis, this has been defined in the protocol as the final analysis (protocol amendment 1 and 2). However, it is uncertain how this affects the continuance and maintaining the blinding of the study. In addition, this is important to gain information on the persistence of protection during the 24 months follow-up and the potential need for further booster immunisation or revaccination.

The humoral immunogenicity results showed that the RSV mRNA-1345 vaccine is able to induce a durable immune response in the intended target population. In addition, evidence of a robust and persistent RSV preF-specific T cell response was demonstrated through a follow up period of 3 months.

Waning of immunity in terms of nAbs and binding Abs is demonstrated overtime until Month 12 with neutralising antibodies (GMTs) still higher than baseline. However, the immune response observed cannot be directly translated to efficacy as there is no correlate of protection. The immunogenicity data from Study P301 have been provided in the applicant's D120 responses.

Comparisons of immunogenicity across studies were not possible at this point of time, as further data with a later cut-off are required.

The safety database for the exposure with mRNA-1345 with a median follow-up time was 257.0 days (range: 1 to 530 days) in Study P301 is sufficient for an adequate assessment of the vaccines safety profile. Approximately 7.9% were 80 YOA or older, which does not meet the enrolment target of 10% participants ≥80 years of age. However, this is acceptable.

The mRNA-1345 vaccine shows an acceptable safety profile, primarily characterised by mild to moderate reactogenicity reactions. The most common AEs were injection site pain, fatigue, headache, and myalgia, while SAEs and AESIs were rare in both the vaccine and placebo groups. No related cases of Myocarditis/pericarditis were reported, but myocarditis/pericarditis still remains an important potential concern. Participants with severe immunodeficiency, autoimmune diseases, or inflammatory diseases were excluded from the studies, leaving a gap in safety information for these populations. However, this is listed as missing information in the RMP and post-authorisation studies in these populations (study mRNA-1345-P303, -P902 and -P03) are planned as part of the pharmacovigilance plan. No studies have been conducted regarding interaction with other vaccines, which will require further post-authorisation data collection.

3.7.2. Balance of benefits and risks

The pivotal clinical study met the primary efficacy and safety endpoints based on a pre-specified interim analysis, as well as in an additional analysis. The immunogenicity data from the Study P301 up to D29 have been provided in the applicant's D120 responses, however, results from additional later time points are required. Cell-mediated immunity has only been assessed in a separate clinical study as an exploratory endpoint.

The mRNA-1345 vaccine is mildly reactogenic and generally well-tolerated in the intended target population. Updated safety data with longer follow-up time, and additional data in at-risk subjects as requested have been provided.

The available clinical data for the RSV mRNA vaccine indicates the benefit of the RSV mRNA vaccine in adults 60 years of age and older.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of mResvia is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of mResvia is favourable in the following indication(s):

> *"mRESVIA is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in adults 60 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations."*

The CHMP therefore recommends the granting of the marketing authorisation subjects to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

New active substance status

Based on the CHMP review of the available data, the CHMP considers that single-stranded 5' capped mRNA encoding the respiratory syncytial virus glycoprotein F stabilised in the prefusion conformation, contained in the medicinal product mResvia is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.